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Health and Environmental Effects Profile for Xylenes (o-, m-, p-)

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16. ABSTRACT

The Health and Environmental Effects Profile for Xylenes (o-, m-, p-) was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Xylenes has been determined to be a systemic toxicant. A Reference Dose (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for xylenes is 1.8 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for xylenes is 1000.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

o-Xylene, m- and p-xylene are colorless liquids with characteristic odors. The xylenes are important commercial compounds because of their use in the blending of gasolines and in chemical synthesis. In 1984, the total U.S. production of mixed xylenes was 6.49 billion pounds; p-xylene production was reported to be 4.26 billion pounds and o-xylene production was 0.69 billion pounds (USITC, 1985). About 96% of industry capacity to produce mixed xylene streams is based on catalytic reformate feedstock from petroleum refining (SRI, 1985). The bulk of the xylenes produced in catalytic reformate are blended into gasoline (Ransley, 1984) and are not separated as an isolated mixed xylene stream. The isolated mixed xylene streams are used for the separation of the individual xylene isomers (74.9%), gasoline blending (13.2%), solvent applications (8.8%) and ethylbenzene isolation (3.1%) (Ransley, 1984). p-Xylene is used almost exclusively for the production of terephthalic acid and dimethyl terephthalate for polyester production (CMR, 1983a), while o-xylene is used almost entirely in the synthesis of phthalic anhydride (CMR, 1983b). m-Xylene is used for the manufacture of isophthalic acid and isophthalonitrile (Ransley, 1984).

Volatilization and microbial degradation are the important environmental fate processes for the xylenes in water. Experimentally measured Henry's Law constants (Hine and Mookerjee, 1975) can be used to predict volatilization half-lives of ~3 hours from a body of water 1 m deep (Lyman et al., 1982); volatilization half-lives of 1.5-7 days have been estimated for xylenes in rivers, ponds and lakes (Smith and Harper, 1982). Significant microbial transformation of the xylenes has been demonstrated in laboratory

studies using groundwaters and seawater as inocula (Kuhn et al., 1985; Kappeler and Wuhrmann, 1978; Van der Linden, 1978). Various BOD and activated sludge seed tests (Sasaki, 1978; Kitano, 1978; Bridie et al., 1979a) and numerous pure culture studies have also demonstrated the biodegradability of the xylenes.

Once exposed to the ambient atmosphere, the xylenes should be rapidly removed by reaction with hydroxyl radicals. Based on the recommended values of the rate constants for the hydroxyl radical reactions (Atkinson, 1985), the half-lives of the xylenes in typical atmospheres can be calculated to be 7.9-13.1 hours. Xylene can be effectively washed out of air by raindrops (Tada et al., 1979) and has been detected in rainwater (Kawamura and Kaplan, 1983).

Xylenes have been detected in drinking waters, groundwaters, surface waters, leachates and industrial effluents. The U.S. EPA's Groundwater Supply Survey detected xylene in ~2% of 945 finished water supplies using groundwater sources throughout the United States (Westrick et al., 1984). The sources of xylene exposure to natural waters include leaching from waste dumps and contaminated soil, industrial effluents and removal of xylene from the atmosphere by rainfall. Xylene has been detected in human breast milk (Pellizzari et al., 1982) and coffee (Wang et al., 1983). Xylene has been detected in ambient atmospheres throughout the United States and the world. Automobile exhaust is considered the major emission source of xylene to the atmosphere (Singh et al., 1981a). Other sources of xylene emission to air include its production and use as an intermediate, gasoline blending and distribution, decomposition product in iron foundries, evaporation during solvent applications, forest fires and coal pyrolysis (Weant and McCormick, 1984; Felder and Gilman, 1984).

Naturally adapted soil microbes are capable of biodegrading o- and m-xylene (Wilson et al., 1983). Soil adsorption studies have indicated that o-xylene (Nathwani and Phillips, 1977) and p-xylene (Schwarzenbach and Westall, 1981) are mobile in various soil types. The widespread occurrence of the xylenes in groundwaters (Westrick et al., 1984) suggests that leaching is important.

The limited acute toxicity data for the three xylene isomers do not indicate a clear trend in relative toxicity. Rainbow trout and striped bass were the most sensitive fish species tested, with 96-hour LC_{50} values of 10 mg/ℓ (Folmar, 1976) and 2-11 mg/ℓ (Benville and Korn, 1977), respectively. The larvae of rainbow trout appeared to be more sensitive to xylene than eggs or fry (Black et al., 1982). Among the invertebrate species tested, crustaceans, with LC_{50} values of 1-10 mg/ℓ, were generally more sensitive than insects, molluscs or protozoa. There was little information available concerning chronic toxicity, plant effects or residues of xylene in aquatic biota.

Data on the pharmacokinetics of xylenes following oral exposure are limited. Inhalation and dermal exposures, however, have been more completely studied.

Based on data that rabbits orally dosed with o-, m- or p-xylene excreted 85-90% of the dose as metabolites in the urine (Bray et al., 1949), absorption of xylenes from the gastrointestinal tract appears complete. Pulmonary absorption by humans is ~64% efficient (Astrand et al., 1978; Riihimaki et al., 1979a,b; Sedivec and Flec, 1974, 1976; Gamberale et al., 1978; Senczuk and Orlowski, 1978). Absorption of xylene vapor through the skin is much slower than pulmonary absorption and appears to represent 1-2% of that absorbed through the lungs (Riihimaki and Pfaffli, 1978). Absorption as high as 9.6 mg/cm²/hour for pure xylene applied to the forearm was reported (Dutkiewicz and Tyras, 1968).

Distribution of xylene throughout the body appears rapid (Carlsson, 1981). Bioaccumulation may occur in the adipose tissue during high-level or extended xylene exposure, but most xylene is cleared rapidly from the body since it is metabolized. The half-life of m-xylene in adipose tissue following exposure to 100 ppm (434 mg/m³) 6 hours/day for 6 days was 47.5 hours (Engstrom and Riihimaki, 1979). Savolainen et al. (1979) reported that accumulation of xylene in the perirenal fat of rats exposed by inhalation was initially high after 5 weeks of exposure but decreased with longer exposure durations.

In animals and humans, xylene isomers are predominantly (85-95% of absorbed dose) metabolized by oxidation of one of the methyl groups, yielding toluic acid, which is then conjugated for urinary excretion. Evidence from animal and human studies indicates that both m- and p-toluic acid metabolites are conjugated with glycine forming m- or p-methylhippuric acid, respectively. In animals, o-toluic acid conjugates equally well with glucuronide, resulting in both o-methylhippuric and o-toluyl glucuronide in the urine. In humans, o-toluic acid appears to be conjugated primarily with glycine so that o-methylhippuric acid predominates. Aromatic hydroxylation of all xylene isomers represents a minor (1-2%) metabolic pathway in animals and humans.

Elimination of xylenes is primarily through urinary excretion of metabolites, which may represent ~95% of the absorbed dose. Exhalation of unchanged xylene from the lungs may represent <5% of the absorbed dose. In humans exposed to m-xylene by inhalation at 600 mg/m³ (138 ppm) for 8 hours, the maximal urinary excretion rate was 350 mg/hour. Excretion rate was related to the absorbed dose and did not appear to be saturated at this level of exposure (Senczuk and Orlowski, 1978). Excretion was nearly complete within 30 hours of exposure and the chance for accumulation was slight. Urinary elimination was described as a three-phase process, with respective half-times at 1-2, 10 and 20 hours. The slowest phase only became evident after prolonged xylene exposure, possibly indicating clearance of accumulated xylene from the adipose tissue (Riihimaki et al., 1979a,b). Pulmonary elimination was a two-phase process, with half-times of 0.5-1 and 20 hours, respectively.

Xylenes (mixed isomers) have been tested for carcinogenicity in rats treated with 0, 250 and 500 mg/kg/day and mice treated with 0, 500 and 1000 mg/kg/day by gavage, 5 days/week for 103 weeks (NTP, 1986). Increased incidence of interstitial cell tumors in male rats were thought not to be compound-related and NTP (1986) reported that no compound-related evidence of carcinogenicity was found. Berenblum (1941) reported that xylene was not carcinogenic in skin-painting experiments in mice. Pound (1970) obtained negative results in initiation-promotion experiments with xylene as the initiator and croton oil as the promotor. Arp et al. (1983) reported that of 15 cases of leukemia in a cohort of 6678 workers in the rubber industry, 6 of the cases occurred in employees that were exposed to coal-tar derived naphtha, which is composed primarily of xylene. Exposure levels were not quantified. Based on matched case-control results, the relative risk estimate was 5.5 ($p<0.02$); however, the data are inadequate to assess the relative risk of xylene, because workers were exposed to a mixture of solvents and the sample size was small. Olsson and Brandt (1981) observed an increased incidence of non-Hodgkin's lymphoma in solvent-exposed workers; however, since exposure was to mixed solvents, this effect could not be attributed to xylene alone.

The results of carcinogenicity testing in animals are inadequate to assess the carcinogenic potential of xylenes. The data of Arp et al. (1983) provided inadequate evidence from which to evaluate the human carcinogenic potential of xylenes. Using EPA's guidelines for carcinogen risk assessment, xylene is placed in EPA Group D, meaning there is inadequate evidence to assess the carcinogenic potential of this compound. A potency factor could not be calculated because quantitative exposures were lacking.

Xylene does not appear to be mutagenic in bacterial assays nor active in short-term mammalian cell assays. Mutagenicity testing of xylene in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 yielded negative results with or without metabolic activation (Florin et al., 1980; Bos et al., 1981; NTP, 1986). Negative results were also obtained in the rec assay tests in *Escherichia coli* (McCarroll et al., 1981). m- and o-Xylene were negative in the *D. melanogaster* recessive lethal test; whereas, technical xylene was weakly mutagenic. Xylene did not cause chromosomal aberrations in rats (Donner et al., 1980), and the number of chromosomal aberrations greater than control levels were not observed in a group of 17 painters exposed to xylene and 10 other solvents (Haglund, et al., 1980). The number of SCEs and structural chromosome aberrations in human lymphocytes treated with xylene *in vitro* was not significantly different from controls (Gerner-Smidt and Friedrich, 1978).

Xylene appears to be a teratogen in animals when administered by inhalation and the oral route. Marks et al. (1982) administered xylene by gavage to female mice on days 6-15 of gestation. At doses ≥ 2.06 g/kg/day, an increased incidence of cleft palate, decreased fetal weights and a significant increase in percent malformations ($p<0.05$) were observed. Maternal toxicity was also observed at these doses. The incidence of these effects was reduced at doses of 1.03 g/kg/day. Nawrot and Staples (1981) gavaged mice with either o-, m- or p-xylene 3 times/day during days 6-15 of gestation at levels of 780, 1960 and 2610 mg/kg/day. Signs of maternal toxicity and cleft palates in offspring occurred at the two highest doses of the o- and p-isomers and at the highest dose of m-xylene.

Shigeta et al. (1983) treated mice by inhalation with xylene at levels of 0, 500, 1000, 2000 and 4000 ppm (0, 2171, 4342, 8684 and 17,369 mg/m³), 6 hours/day during days 6-12 of gestation, and observed a dose-related delay of sternebrae ossification at 2000 ppm. Hudak and Ungvary (1978) exposed pregnant CFY rats to 1000 mg/m³ mixed xylenes continuously during days 9-14 of gestation, and observed a statistically significant increased incidence of fused sternebrae and extra ribs. Ungvary et al. (1980a) exposed rat dams to one of the xylene isomers (o-, m-, p-) continuously from days 7-14 of gestation at levels of 150, 1500 and 3000 mg/m³. Signs of maternal toxicity were observed at 1500 mg/m³ for the o-isomer and at 3000 mg/m³ for the m- and p-isomers. At 3000 mg/m³ o-xylene, skeletal retardation was observed, and at 3000 mg/m³ m-xylene, a significant ($p<0.01$) decrease in fetal weight was observed. Skeletal retardation was observed at all doses of the p-isomer. Balogh et al. (1982) exposed rats to 230, 1900 or 3360 mg/m³, continuously on days 7-14 of gestation, and observed delayed bone development at all three dose levels. Mirkova et al. (1983) exposed rats to a xylene mixture at levels of 0, 10, 50 or 500 mg/m³, and observed postimplantation losses and delayed ossification at 50 and 500 mg/m³. Teratogenic effects (hydrocephalus, microphthalmic aortal dilatation) were observed at 500 mg/m³. Bio/Dynamics (1982) exposed both sexes of rats to 0 and 2171 mg/m³, 6 hours/day for 130 days before mating, during the mating period and on days 1-20 of gestation (females only), and observed variations in ossification and reduced female fetal weight in the offspring. Litton Bionetics (1978b) exposed rats to 0, 435 and 1737 mg/m³, 6 hours/day on days 6-15 of gestation, and observed a significant increase in retarded ossification at the high dose.

In an extensive reproduction study, male and female rats were exposed by inhalation to a xylene mixture at 0, 60, 250 or 500 ppm (0, 261, 1086 or 2171 mg/m³), 6 hours/day for 130 days before mating, during the mating period, on days 1-20 of gestation (females only) and on days 5-20 of lactation (females) (Bio/Dyanmics, 1982). The only treatment-related effects were reduced pup weights and decreased mean ovary weights of female pups at day 21 after birth at 500 ppm.

Several studies concerning the toxicity of xylene by the oral and inhalation routes were located in the available literature. A dose-related increased mortality was observed in male rats treated by gavage with mixed xylenes at 250 and 500 mg/kg/day, 5 days/week for 103 weeks; the increase was statistically significant at the high dose (NTP, 1986). Many of the deaths were caused by gavage errors, but the possibility that the dosed rats resisted dosing by gavage because of a behavioral effect was not ruled out. High-dose male rats also had reduced body weight gain. Male and female mice similarly treated at 1000 mg/kg/day were consistently hyperactive for 5-30 minutes after dosing from week 4-103. In a 13-week gavage study, male and female rats treated with 1000 mg/kg/day mixed xylenes, 5 days/week had reduced body weight gain, while male and female mice treated with 2000 mg/kg/day had signs of CNS toxicity after dosing and reduced body weight gains (NTP, 1986). Bowers et al. (1982) gave male rats o-xylene at a dietary level of 200 ppm for up to 6 months and observed ultrastructural hepatocyte changes.

Induction of hepatic enzymes, hepatotoxicity and hepatomegaly were observed in male rats exposed to 4750 mg/m³ o-xylene, 8 hours/day, 7 days/week for 1 year (Tatrai et al., 1980, 1981). Jenkins et al. (1970) exposed dogs, monkeys, guinea pigs and rats to 337 and 3358 mg/m³ o-xylene, 8 hours/day, 5 days/week for 6 weeks. No significant effects were observed in the dogs, monkeys or guinea pigs; however, 1 and 3 of 12-14 rats died in the low- and high-dose groups, respectively. Tatrai and Ungvary (1980) exposed male rats to 3500 ppm o-xylene [U.S. EPA (1984) questioned this level and suggested that the level should be 3500 mg/m³] for 8 hours/day, 7 days/week (presumably) for 6 weeks and observed decreased body weight, hepatomegaly and ultrastructural changes. Smyth and Smyth (1928) exposed guinea pigs to 300 ppm (1300 mg/m³) m-xylene, 4 hours/day, 6 days/week for 10 or 11 weeks. Pulmonary inflammation and slight degeneration of the liver were observed in the guinea pigs exposed for 10 weeks. Moderate renal tubular degeneration and two cases of pulmonary inflammation were observed in guinea pigs exposed for 11 weeks. Savolainen et al. (1979a) and Savolainen and Pfaffli (1980) exposed male rats to 212, 1710 and 3220 mg/m³ m-xylene, 6 hours/day, 5 days/week for 2 and 18 weeks. The rats exposed to 212 and 1710 mg/m³ had decreased brain glutathione and increased brain NADPH diaphorase. The rats treated at the highest dose had decreased brain glutathione and superoxide dismutase and increased NADPH diaphorase. Azoreductase activity was increased at the middle and high dose. No effects were observed in mice or rats exposed by inhalation to p-xylene at 5300 mg/m³ or in rats exposed to 4300 mg/m³ m-xylene or 7300 mg/m³ o-xylene, 8 hours/day for 14 days (Cameron et al., 1938). Carpenter et al. (1975) observed no effects in rats or dogs exposed to mixed xylenes at up to 3500 mg/m³, 6 hours/day, 5 days/week for 13 weeks. Fabre et al. (1960)

reported renal lesions, vascular congestion of several organs and bone marrow hyperplasia in rats and rabbits exposed by inhalation to 3000 or 5000 mg/m³. Renal tubular dilatation and epithelial regeneration were observed in rats but not dogs exposed to mixed xylene at 3000 or 6000 mg/m³.

Human occupational exposure to solvents including xylene, benzene and toluene has been associated with decreased uric acid excretion (Mikulski et al., 1972), impairment of renal function (Askergren et al., 1981a,b; Askergren, 1981, 1982), ophthalmological and neurophysiological effects (Kurppa and Husman, 1982), leukocytopenia (Sukhanova et al., 1969) and other hematological effects (Moszychzynski, 1981, 1982) and liver damage (Dossing et al., 1983). Results of laboratory experiments on human subjects exposed acutely by inhalation to ≥100 ppm (435 mg/m³) to xylene suggest that 100 ppm is the threshold for toxicity (Nelson et al., 1943; Carpenter et al., 1975; Riihimaki and Savolainen, 1980), although sensitive individuals may experience eye and upper respiratory tract irritation (Hake et al., 1981). The odor threshold is ~1 ppm (4.3 mg/m³) (Carpenter et al., 1975).

An RfD of 1.8 mg/kg/day was calculated from a rat NOAEL of 250 mg/kg/day (5 days/week) in a 2-year gavage study by NTP (1986). An uncertainty factor of 100 was used. Higher doses resulted in possible behavioral effects and increased mortality. An RQ of 1000 was calculated based on increased mortality in rats treated by gavage with 500 mg/kg/day in the NTP (1986) study.

The RfD of 1.8 mg/kg/day should be considered as provisional and will be reviewed and revised if appropriate pending the results of ongoing subchronic oral testing by OSW of individual isomers and OTS testing of mixed xylenes.

Subchronic and chronic inhalation studies of both mixed xylenes and individual isomers have not demonstrated adverse histopathological effects in adult animals. However, altered hepatic and brain enzyme activities have been reported in rats exposed to o- and m-xylenes at 4750 and 3500 mg/m^3, respectively. The available teratogenic and developmental inhalation data indicate that both mixed xylenes and individual xylene isomers can adversely affect the conceptus at doses that are maternally toxic. The most pronounced effects of inhalation exposure are skeletal retardation (o-xylene at 1500 mg/m^3) and decreased neonatal survival (p-xylene at 3000 mg/m^3). Inhalation effects observed for humans range from lethality at extremely high doses ($\geq$10,000 ppm or 435,000 mg/m^3) to nausea, dizziness and eye, nose and throat irritation (20-200 ppm or 87-870 mg/m^3). Clinical studies have shown that inhalation exposure to mixed xylenes $\leq$300 ppm (1305 mg/m^3) does not result in any adverse neurobehavioral effects.

Similar results have been reported in chronic and subchronic oral studies with mixed xylenes and the individual xylene isomers in rats and mice. A rat NOAEL of 250 mg/kg/day for 5 days/week was determined in a 2-year gavage study by NTP (1986); higher doses resulted in behavioral effects and increased mortality. An RfD of 1.8 mg/kg/day (126 mg/day), which is protective against adverse effects from inhalation or oral exposure to xylenes, has been recommended.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
av.	Average
BCF	Bioconcentration factor
BOD	Biological oxygen demand
BODT	Biological oxygen demand, theoretical
BUN	Blood urea nitrogen
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients
EEG	Electroencephalogram
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RNA	Ribonucleic acid

LIST OF ABBREVIATIONS (cont.)

SAP	Serum alkaline phosphatase
SCE	Sister chromatid exchange
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMR	Standard mortality ratio
STEL	Short-term exposure level
TLV	Threshold limit value
TWA	Time-weighted average
VEP	Visual evoked potentials
VER	Visual evoked response
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The structures, CAS Registry numbers, molecular weights and empirical formulas of the xylene isomers are presented in Table 1-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Selected physical properties of the xylene isomers are listed in Table 1-2. All three isomers are soluble in alcohol, benzene, ether or acetone (Weast, 1985). They are colorless liquids (Verschueren, 1983) with characteristic odors.

Xylene can undergo chemical reactions involving the position of methyl groups, reactions of the methyl groups and reactions on the benzene ring (Ransley, 1984). The reactions involving the position of methyl groups include isomerization, disproportionation and dealkylation. Reactions of the methyl group include oxidation; oxidation of o-xylene yields phthalic anhydride while oxidation of p-xylene can form terephthalic acid or dimethyl terephthalate.

Xylene is produced in various commercial grades. About 70% of all the mixed xylene grades produced commercially in 1984 had a purity of 98-100% while the remainder had a purity of 90-97.9% (USITC, 1985). In addition to the three xylene isomers, ethylbenzene and toluene are present in commercial mixed xylenes. The purity required depends upon the intended use such as gasoline blending, solvents or isomer separation. The typical mol% purity of p-, m- and o-xylene when they are isolated as end-products are 99.1, 98.5 and 96.0%, respectively (Ransley, 1984).

1.3. PRODUCTION DATA

U.S. production of mixed xylenes totalled 6.49 billion pounds in 1984; production of p-xylene was reported to be 4.26 billion pounds while o-xylene production was reportedly 0.69 billion pounds (USITC, 1985).

TABLE 1-1

The Structures, Synonyms, Empirical Formula and CAS Numbers for Xylenes

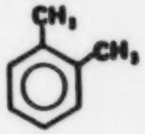
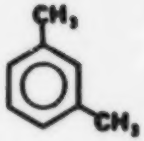
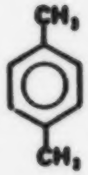
Xylene Isomer (synonyms)	Empirical Formula	Molecular Weight	CAS Registry Number	Structure
o-Xylene 1,2-dimethylbenzene o-methyltoluene o-xylol	C_8H_{10}	106.167	95-47-6	
m-Xylene 1,3-dimethylbenzene m-methyltoluene m-xylol	C_8H_{10}	106.167	108-38-3	
p-Xylene 1,4-dimethylbenzene p-methyltoluene p-xylol	C_8H_{10}	106.167	106-42-3	

TABLE 1-2

Selected Physical Properties of o-, m- and p-Xylenes

Property	o-Xylene	m-Xylene	p-Xylene	Reference
Boiling point, °C	144.41	139.12	138.37	Ransley, 1984
Freezing point, °C	-25.182	-47.872	13.263	Ransley, 1984
Density (g/cm^3) at 25°C	0.8802	0.8642	0.8610	Ransley, 1984
	0.876	0.860	0.857	NRC, 1981
Refractive Index, 25°C	1.5054	1.4971	1.4958	Ransley, 1984
Log K_{ow}	3.12	3.20	3.15	Hansch and Leo, 1985
Vapor pressure, mm Hg				
at 25°C	6.62	8.25	8.78	MacKay and Shui, 1981
at 20°C	5	6	6.5	Verschueren, 1983
Water solubility, ppm at 25°C	175	NA	NA	McAuliffe, 1963
	170.5	146	156	Sutton and Calder, 1975
	NA	196	198	Bohon and Claussen, 1951
	220.8	160.3	214.5	Tewari et al., 1982
Seawater solubility, ppm at 25°C	129.6	106.0	110.9	Sutton and Calder, 1975
Air conversion factors				
1 mg/m^3	0.23 ppm	0.23 ppm	0.23 ppm	Verschueren, 1983
1 ppm	4.34 mg/m^3	4.34 mg/m^3	4.34 mg/m^3	

NA = Not available

At present, the U.S. production capacity for mixed xylenes is ~11 billion pounds/year (SRI, 1985). About 96% of the industry production capacity is based on catalytic reformate feedstock from petroleum refining, while 2.0% is based on toluene disproportionation, 1.8% on pyrolysis gasoline feed, and <0.3% from coke-ovens (SRI, 1985). Twenty-three U.S. companies operating at 29 locations produce mixed xylenes (SRI, 1985).

Individual isomers can be separated from the mixed xylene streams by crystallization, fractionation and isomerization operations (Ransley, 1984). Table 1-3 lists the U.S. producers of p-xylene and o-xylene. The only U.S. producer of isolated m-xylene is Amoco Chemical (Standard Oil-Indiana) in Texas City, TX (SRI, 1985); Amoco produced ~86 million pounds of m-xylene in 1980 (Ransley, 1984).

1.4. USE DATA

The bulk of the xylenes produced in catalytic reformate are blended into gasoline (Ransley, 1984). These xylenes are generally not separated from the reformate as a mixed xylene stream; therefore, production of these xylenes are not included in the production figures for mixed xylenes. The use pattern for the mixed xylene stream that is separated as a product was reported as follows for 1980 (Ransley, 1984):

p-xylene separation	61.7%
o-xylene separation	12.3%
m-xylene separation	0.9%
gasoline blending	13.2%
solvents	8.8%
ethylbenzene separation	3.1%

As a solvent, xylene is used in the paint and coatings industry (Table 1-4), but this use is likely to decline in the United States because of efforts to reduce hydrocarbon emissions to the air and a tendency of the paint industry to move toward water-based latex paints (Ransley, 1984).

TABLE 1-3

U.S. Producers of o-Xylene and p-Xylene*

Producer	Location	Annual Capacity (10^6 pounds)	
		o-Xylene	p-Xylene
Atlantic Richfield (ARCO)	Houston, TX	220	390
Chevron	Pascagoula, MI	NP	500
DuPont	Chocolate Bayou, TX	30	NP
Exxon	Baytown, TX	269	750
Koch Refining	Corpus Christi, TX	110	390
Phillips Petroleum	Guayama, PR	130	470
Shell Oil	Deer Park, TX	125	NP
St. Croix Petrochem.	St. Croix, VI	NP	600
Standard Oil Ind. (Amoco)	Decatur, AL Texas City, TX	NP NP	1300 900
Tenneco	Chalmette, LA	155	140

*Source: SRI, 1985

NP = Not produced

TABLE 1-4

Uses and Estimated Consumption of Xylene in 1984*

Use	Amount Used (10^6 lb)
Mixed Xylenes	
Production of isomers	6136
Fuel backblending	172
Solvent for paints and coating	436
Other solvents	228
m-Xylene	
Isophthalic acid	67
Solvent and other	NE
o-Xylene	
Phthalic anhydride	683
Other	190
p-Xylene	
Dimethylterephthalate	2065
Terephthalic acid	1530
Other	27

*Source: SRI, 1985

NE = Not estimated

The xylenes are also used in the production of xylene sulfonic acids for use as surfactants.

p-Xylene, commercially the most important xylene isomer, is used almost exclusively for the production of terephthalic acid and dimethyl terephthalate for polyester production (CMR, 1983a; Ransley, 1984). Small amounts are used for solvents and coatings or for pesticides.

o-Xylene is used almost entirely as a feedstock for phthalic anhydride manufacture (Ransley, 1984; CMR, 1983b). Small amounts are used in pesticide and other chemical production, and as a solvent.

m-Xylene is used for the manufacture of isophthalic acid and to a lesser extent, isophthalonitrile (Ransley, 1984).

1.5. SUMMARY

o-Xylene, m- and p-xylene are colorless liquids with characteristic odors. The xylenes are important commercial compounds that are used in the blending of gasolines and in chemical synthesis. In 1984, the total U.S. production of mixed xylenes was 6.49 billion pounds with p-xylene production of 4.26 billion pounds and o-xylene production of 0.69 billion pounds (USITC, 1985). About 96% of industry capacity to produce mixed xylene streams is based on catalytic reformate feedstock from petroleum refining (SRI, 1985). The bulk of the xylenes produced in catalytic reformate are blended into gasoline (Ransley, 1984) and are not separated as an isolated mixed xylene stream. Isolated mixed xylene streams are used for the separation of the individual xylene isomers (74.9%), gasoline blending (13.2%), solvent applications (8.8%) and ethylbenzene isolation (3.1%) (Ransley, 1984). p-Xylene is used almost exclusively for the production of terephthalic acid and dimethyl terephthalate for polyester production (CMR, 1983a), while o-xylene is used almost entirely in the synthesis of phthalic anhydride (CMR, 1983b). m-Xylene is used for the manufacture of isophthalic acid and isophthalonitrile (Ransley, 1984).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Pertinent data regarding the hydrolysis of the xylene isomers could not be located in the available literature as cited in the Appendix.

2.1.2. Oxidation. The rate constant for the reaction between hydroxyl radical and p- or o-xylene in aqueous solution is 7×10^{9} M^{-1} sec^{-1} at room temperature, while the rate constant for m-xylene is 2.3×10^{9} M^{-1} sec^{-1} (Guesten et al., 1981). Assuming the average hydroxyl radical concentration of natural waters to be 10^{-17} M, half-lives of 115 and 350 days can be calculated for p- or o-xylene, and m-xylene.

Reaction with other oxidants, such as alkyl peroxy radicals or singlet oxygen, is not judged to be environmentally important.

2.1.3. Photolysis. The absorption spectra for m- and p-xylene show no absorption of wavelength >290 nm (Sadtler, 1960), indicating that direct photolysis will not occur in the environment. o-Xylene shows weak absorption of wavelengths from 290-320 nm (Sadtler, 1966). In a gas-phase photolysis study, Hustert and Parlar (1981) found that significant photolysis of o-xylene did not occur above 300 nm; therefore, direct photolysis of o-xylene in water is not expected to occur.

2.1.4. Microbial Degradation. Kuhn et al. (1985) examined the microbial transformation of the xylenes in a laboratory system designed to simulate transport of organic compounds under saturated groundwater flow conditions. All three isomers were found to be biodegraded under both aerobic and denitrifying conditions; the m- and p-isomers were degraded at a rate significantly faster than the o-isomer.

Kappeler and Wuhrmann (1978) measured the microbial degradation of the xylenes in a sand percolation column using the mixed microflora of clean groundwater as inoculum. At 10°C, a 5-day lag period was observed before degradation began and complete degradation was accomplished 3 days later; again, degradation of o-xylene was somewhat slower than the other isomers. At 25°C, a 1-day lag period was noted.

Van der Linden (1978) used an artificial seawater inoculated with North Sea coast water to demonstrate moderate degradation of the xylenes. Based on the biodegradation behavior of the xylenes in other natural systems, Wilson and McNabb (1983) have predicted that the xylenes will probably be biotransformed in water-table aquifers.

Using the Japanese MITI test, which uses an activated sludge seed, the xylenes were found to be significantly biodegraded during a 2-week inoculation period (Sasaki, 1978; Kitano, 1978). Bridie et al. (1979a) conducted standard 5-day BOD tests with the xylenes; as a percentage of theoretical oxygen demand, o-, p- and m-xylene were found to have BODTs of 52-57, 80 and 44-78%, respectively. Heukelekian and Rand (1955) found no biodegradation of the xylenes in BOD tests using sewage seed. The xylenes were found to be readily degraded in various activated sludge tests (Malaney and McKinney, 1966; Grunwald et al., 1978) and poorly degraded in others (Marion and Malaney, 1964; Ishihara and Nakajima, 1978). p-Xylene was found readily degradable in an aniline-acclimated activated sludge, but m- and o-xylene were poorly degraded in the same sludge (Malaney, 1960).

The biodegradation of the xylenes has been examined in many pure culture studies. Various species and strains of *Corynebacterium*, *Pseudomonas*, *Nocardia*, *Mycobacterium rhodochrous*, *Vibrio*, *Bacillus*, *Candida*, *Arthrobacter*, *Cladosporium resinae*, *Flavobacterium* and *Bacterium toluolicum* are able to degrade the xylenes either by using xylene as the sole carbon and energy source or by co-oxidation/cometabolism mechanisms (Walker et al., 1973; McKenna, 1976; Ribbons and Eaton, 1982; Fuhs, 1961; Cofone et al., 1973; Bosle and Mavinkurve, 1980; Kunz and Chapman, 1981; Nozaka, 1971; Buswell and Jurtshuk, 1969; Perry, 1979; Nozaka and Kusunose, 1968; Raymond et al., 1967; Gibson et al., 1974; Gibson, 1978; Davey and Gibson, 1974; Atkinson and Newth, 1968; Omori and Yamada, 1969; Skryabin et al., 1977). The oxidative products of xylene degradation have been shown to be the corresponding toluic acid isomers (Atkinson and Newth, 1968), dimethylpyrocatechols, methylcatechols and tolualdehydes (Gibson et al., 1974; Davey and Gibson, 1974; Perry, 1979).

2.1.5. **Volatilization.** Hine and Mookerjee (1975) experimentally measured the equilibrium concentrations of the xylene isomers in the water-to-gas phase of dilute aqueous solutions at 25°C. From these measured concentrations, the following Henry's Law constants are calculated: o-xylene, 5.3×10^{-3} atm•m^3/mol; m- and p-xylene, 6.2×10^{-3} atm•m^3/mol. These Henry's Law constants derived from experimental data are very close to the values calculated by dividing the vapor pressures by the water solubilities. Henry Law constants of $5.3\text{-}6.2\times10^{-3}$ atm•m^3/mol indicate that volatilization is rapid in the environment (Lyman et al., 1982); the volatilization half-life of o-xylene from a body of water 1 m deep can be calculated to be 3.2 hours (Lyman et al., 1982).

Smith and Harper (1982) experimentally measured the volatilization rates of fuel components dissolved in water. Based on the experimentally measured mass transfer rates, the authors estimated the volatilization half-lives in the environment to be 7 days in ponds, 1.5 days in rivers and 6 days in lakes with respect to the substituted benzene components which included the xylenes.

2.1.6. **Adsorption.** Soil adsorption data suggest that adsorption of the xylenes to particulate organic matter and sediment in water is not expected to be a significant environmental fate process (Section 2.3.3.)

2.1.7. **Bioaccumulation.** Ogata and Miyake (1978) measured the bioconcentration of xylenes in eels, *Anguilla japonica*, using a crude oil suspension. The eels were reared in the crude oil suspension (50 ppm) for 10 days; after 10 days, the concentration ratio of xylene in eel tissue to xylene in the water yielded the following BCFs: o-xylene, 21.4; m-xylene, 23.6; p-xylene, 23.6. After the eels were transferred to clean seawater, xylenes in the eel tissue were found to have a half-life of 2.0-2.6 days.

Nunes and Benville (1979) exposed the Manila clam, *Tapes semidecussata*, to the water soluble fraction of crude oil for 8 days in a flow-through aquarium. The BCFs for m-xylene and o-xylene were found to be 6.4 and 7.3, respectively, in the clam tissue.

Although the Log K_{ow} values of the xylenes suggest a moderate potential for bioaccumulation in aquatic organisms, the above experimental data indicate that bioaccumulation of xylenes is not very significant in the environment.

2.1.8. **Persistence.** Walsh et al. (1977) measured the rate of disappearance of xylene from water in irrigation channels. An initial concentration of 548-760 ppm was found to fall below 100 ppm after the water travelled 10 miles. Although the mechanism for removal was not examined, volatilization was probably responsible for the dissipation.

2.2. AIR

2.2.1. **Reaction with Hydroxyl Radical.** In a review of the experimental data regarding the reaction rate between xylenes and hydroxyl radical in the atmosphere, Atkinson (1985) recommended the following rate constants at

25°C: o-xylene 1.47×10^{-11} cm^3 $molecule^{-1}$ sec^{-1}; m-xylene, 2.45×10^{-11} cm^3 molecule sec^{-1} and p-xylene, 1.52×10^{-11} cm^3 molecule sec^{-1}. Assuming an average atmospheric hydroxyl radical concentration of 10^6 molecules/cm^3, half-lives ranging from 7.9-13.1 hours (for m- and o-xylene, respectively) are calculated, indicating rapid removal in sunlit atmospheres.

The photooxidation products of the xylenes include tolualdehyde, xylenol, glyoxal, methylglyoxal, acetaldehyde, biacetyl and maleic anhydride (Tuazon et al., 1984; Kato, 1981; Takagi et al., 1978).

2.2.2. **Reaction with Ozone.** Pate et al. (1976) determined the following rate constants for the reaction between xylenes and ozone at 24°C: o-xylene, 7×10^{-22} cm^3 $molecule^{-1}$ sec^{-1}; m-xylene, 6×10^{-22} cm^3 $molecule^{-1}$ sec^{-1} and p-xylene, 4×10^{-22} cm^3 $molecule^{-1}$ sec^{-1}. Similar rate data were determined by Atkinson et al. (1982). Assuming an average atmospheric ozone concentration of 10^{12} molecules/cm^3, half-lives >10 years are calculated indicating no environmental significance.

2.2.3. **Reaction with $O(^3P)$.** The rate constants for the reaction between xylenes and $O(^3P)$ at 25°C are as follows: o-xylene, 2.23×10^{-13} cm^3 $molecule^{-1}$ sec^{-1}; m-xylene, 4.19×10^{-13} cm^3 $molecule^{-1}$ sec^{-1}; and p-xylene, 2.25×10^{-13} cm^3 $molecule^{-1}$ sec^{-1} (Ravishankara, 1981). Similar rate data were found by Atkinson and Pitts (1974). Assuming an average atmospheric concentration of 5×10^4 molecules/cm^3, half-lives >5 years are calculated, indicating no environmental significance.

2.2.4. **Reaction with NO_3.** The experimentally determined rate constants for the reaction between xylene and atmospheric NO_3 indicate no importance as an environmental sink (Atkinson et al., 1984).

2.2.5. Photolysis. The xylene isomers do not absorb sunlight or have weak absorption (Sadtler, 1960, 1966). Hustert and Parlar (1981) irradiated the xylenes in vapor-phase with light of wavelength >300 nm, and observed no significant photolysis. Therefore, direct photolysis is not expected to occur in the troposphere.

2.2.6. Physical Removal. m-Xylene and p-xylene have been detected in Los Angeles rainwater at concentrations of 2 and 9 ppb, respectively (Kawamura and Kaplan, 1983), suggesting that this physical removal process may be significant. Tada et al. (1979) have found xylene effectively washed out of air by raindrops.

2.3. SOIL

2.3.1. Microbial Degradation. Wilson et al. (1983) examined the biodegradation of o-xylene and m-xylene in two core material samples taken immediately below a water table to determine if microbes adapted to organic pollutants. One core sample was taken at a creosote waste disposal site where subsoils were exposed to pollutants and the other sample was taken at an unpolluted site. Sterilized core material tests were run as controls. No degradation was observed in both sterilized core materials or in the unsterilized material from the unpolluted site; however, degradation in the sample from the creosote site was relatively rapid, with a degradation rate of ~19% per week and complete degradation within 12 weeks.

The biodegradation of o- and m-xylene in an artificial compost mixture of soil, manure, shredded newspaper, sawdust, peat moss, sludge, powdered milk and fertilizer has been studied (Snell Environmental Group, Inc., 1982). Initial concentrations were reduced 79-81% after a 7-day period.

2.3.2. Chemical Degradation. Although pertinent data specifically regarding the chemical degradation of the xylenes in soil were not located, the lack of degradation in the sterilized core materials of the Wilson et al. (1983) biodegradation study (see Section 2.3.1.) indicates that no chemical degradation occurs. The chemical reactivity of the xylenes suggests that environmental transformation in soils is unlikely.

2.3.3. Adsorption. Nathwani and Phillips (1977) examined the adsorption of hydrocarbon components of crude oil on a variety of soil types in laboratory tests. The tests consisted of spiking a crude oil with o-xylene and measuring the xylene adsorption to soil after exposing the soil to the spiked crude oil. Based on the measured Freundlich constants and organic soil contents, the following K_{oc} values are determined: silty clay = 68, sandy loam = 48 and silty loam = 62. These K_{oc} values are indicative of high soil mobility. Nathwani and Phillips (1977) also found that adsorption increases and desorption decreases as the organic content of the soil increases.

Using a laboratory test with a soil of low organic content, Schwarzenbach and Westall (1981) determined that p-xylene is present primarily in the water-phase rather than the adsorbed-phase at sorption equilibrium, which suggests high soil mobility.

The log K_{ow} values of the xylenes (3.12-3.20) and the water solubilities (140-220 ppm) are suggestive of low-to-medium soil mobility. Predicting the K_{oc} based on the molecular topology and quantitative structure-activity relationship analysis method of Sabljic (1984) yields a K_{oc} value of 350, which is indicative of medium soil mobility.

The widespread occurrence of xylenes in groundwaters (Westrick et al., 1984) suggests that leaching is important.

2.3.4. Volatilization. The relatively high vapor pressures of the xylenes and their tendency to volatilize from water (see Section 2.1.5.) suggests that volatilization from soil may also be important.

2.3.5. **Photolysis.** Since the xylenes do not significantly absorb sunlight, surface photolysis is expected to have little importance.

2.4. SUMMARY

Volatilization and microbial degradation are the important environmental fate processes for the xylenes in water. Experimentally measured Henry's Law constants (Hine and Mookerjee, 1975) can be used to predict volatilization half-lives of ~3 hours from a body of water 1 m deep (Lyman et al., 1982); volatilization half-lives of 1.5-7 days have been estimated for xylenes in rivers, ponds and lakes (Smith and Harper, 1982). Significant microbial transformation of the xylenes has been demonstrated in laboratory studies using groundwaters and seawater as inocula (Kuhn et al., 1985; Kappeler and Wuhrmann, 1978; Van der Linden, 1978). Various BOD and activated sludge seed tests (Sasaki, 1978; Kitano, 1978; Bridie et al., 1979a) and numerous pure culture studies have also demonstrated the biodegradability of the xylenes.

Once exposed to the ambient atmosphere, the xylenes should be rapidly removed by reaction with hydroxyl radicals. Based on the recommended values of the rate constants for the hydroxyl radical reactions (Atkinson, 1985), the half-lives of the xylenes in typical atmospheres can be calculated to be 7.9-13.1 hours. Xylene can be effectively washed out of air by raindrops (Tada et al., 1979) and has been detected in rainwater (Kawamura and Kaplan, 1983).

Naturally adapted soil microbes are capable of biodegrading o- and m-xylene (Wilson et al., 1983). Soil adsorption studies have indicated that o-xylene (Nathwani and Phillips, 1977) and p-xylene (Schwarzenbach and Westall, 1981) are significantly mobile in various soil types. The widespread occurrence of the xylenes in groundwaters (Westrick et al., 1984) suggests that leaching is important.

3. EXPOSURE

3.1. WATER

The xylenes have been detected in drinking waters, groundwaters, surface waters, leachates and industrial effluents (Table 3-1).

Westrick et al. (1984) reported the results of the U.S. EPA's Groundwater Supply Survey that sampled 945 finished water supplies having groundwater sources for the presence of volatile organic compounds. The results, with respect to the xylenes, are listed in Table 3-2; o-xylene was detected in 16 water supplies, while o- and p-xylene were detected in 18 water supplies.

There are several sources for xylene exposure to natural waters. As noted in Table 3-1, xylene has been detected in waste dump leachates and in groundwaters below contaminated areas. In addition, industrial effluents contain xylene. Xylene is a common pollutant in the ambient atmosphere (Section 3.3.) and can be removed from the atmosphere by rainfall (see Section 2.2.6.); this may be a significant source of exposure of xylene to natural waters.

3.2. FOOD

Limited data are available on the detection of xylene in food. Xylene has been detected in human breast milk (Pellizzari et al., 1982), in coffee (Wang et al., 1983) and in black currant oil (Kerslake and Menary, 1985).

3.3. INHALATION

Xylene has been monitored extensively in ambient atmospheres throughout the United States (Table 3-3). Similar atmospheric xylene concentrations have been measured in Japan (Suyama et al., 1980), Great Britain (Clark et al., 1984), the Netherlands (Bos et al., 1977), Australia (Nelson and Quigley, 1982), France (Raymond and Guiochon, 1974), Belgium (Termonia, 1982), Norway (Wathne, 1983) and Germany (Halket and Angerer, 1980).

TABLE 3-1

Xylene Monitoring Data for Environmental Waters

Type of Water	Locations	Concentration (ppb)	Remarks	Reference
Well (drinking)	Tennessee	0.07-1.6	leachate contamination from a pesticide waste dump; all isomers	Clark et al., 1982
Seawater	Gulf of Mexico	0.0027-0.0244 0.0003-0.0101	m- and p-xylene o-xylene	Sauer et al., 1978
Leachates	Kentucky, New York	NR	waste disposal sites; all isomers	Francis et al., 1980
River	Tennessee River	NR	all isomers	Gordon and Goodley, 1971
Drinking	14 sources - UK	NR	all isomers	Fielding et al., 1981
Ground	Oklahoma	0.6-0.9	o-, p-xylene; groundwater below landfill	Dunlap et al., 1976
Drinking	Cincinnati, OH	0.056 0.092 0.092	o-xylene m-xylene p-xylene	Coleman et al., 1984
Drinking	Houston, TX Tuscaloosa, AL	NR	all isomers	Bertsch et al., 1975
Drinking	12 Great Lakes Supplies	0-0.0099	all isomers	Williams et al., 1982
Ground	Texas, Wyoming	260-590 240-830	o-xylene m- and p-xylene; contamination from coal gasification sites	Stuermer et al., 1982
Ground, leachates	Minnesota	950 (maximum)	all isomers	Sabel and Clark, 1983
Seawater	open ocean	0.004-0.030	all isomers	Sauer, 1981
Drinking	Canada	<1 (mean)	all isomers	Olson et al., 1982
Seawater	Vineyard Sound, MA	0.009-0.020 (av.)	all isomers	Gschwend et al., 1982
Drinking	Evansville, IN	NR	all isomers	Kleopfer and Fairless, 1972
Wastewater	NR	2-8	petrochemical plant effluent	Keith, 1974
Seawater	Port Valdez, AL	0-0.7	all isomers	Lysyj et al., 1980

TABLE 3-1 (cont.)

Type of Water	Locations	Concentration (ppb)	Remarks	Reference
Leachate	Ontario, Canada	0-820	landfill leachate	Reinhard et al., 1984
Ground	northeast United States	7-65	all isomers	Rich, 1981
Drinking	Cleveland, OH	NR	all isomers	Sanjivamurthy, 1978
Drinking	Washington, DC	NR	all isomers	Saunders et al., 1975
Drinking	Philadelphia, PA	NR	all isomers	Suffet et al., 1976
Well	Delaware	0.8 (maximum) 1.5 (maximum) 2.9 (maximum)	m-xylene o-xylene, p-xylene; site near solid waste landfill	Dewalle and Chian, 1981
Seawater	Narragansett Bay	NR	all isomers	Wakeham et al., 1983
Ground	Massachusetts, Arkansas	0.05-1.14	all isomers	Hutchins and Ward, 1984
Effluents	United States	<10	chemical manufacture effluents; each isomer	Perry et al., 1979
Surface	United States	NR	one positive detection in 204 samples near heavily industrialized areas across the United States	Ewing et al., 1977
Drink, effluent, river, well, ground	United States	NR	data compilation of various Federal studies	Shackelford and Keith, 1976

NR = Not reported

TABLE 3-2

U.S. EPA Groundwater Supply Survey[a]

Xylene	Number of Random Sites	Occurrences		Concentrations	
		Number of Positives	Percent Positive	Median of Positives (ppb)	Maximum Value (ppb)
m-Xylene	280[b]	6	2.1	0.32	1.5
p-Xylene and o-xylene		6	2.1	0.34	0.59
m-Xylene	186[c]	2	1.1	0.46	0.61
p-Xylene and o-xylene		2	1.1	0.59	0.91
m-Xylene	321[b]	8	2.5	0.38	0.83
p-Xylene and o-xylene		10	3.1	0.44	2.5
m-Xylene	158[c]	0	0	0	0
p-Xylene and o-xylene		0	0	0	0

[a] Source: Westrick et al., 1984

[b] Serves <10,000 persons

[c] Serves >10,000 persons

TABLE 3-3

Atmosphere Monitoring Data for Xylene in the United States

Sampling Location	Concentration (ppb)	Sampling Dates/Remarks	Reference
Los Angeles, CA	4.6 (mean) m-, p-xylene 1.9 (mean) o-xylene	April, 1979	Singh et al., 1981a
Phoenix, AZ	4.2 (mean) m-, p-xylene 1.8 (mean) o-xylene	April-May, 1979	Singh et al, 1981a
Oakland, CA	1.5 (mean) m-, p-xylene 0.8 (mean) o-xylene	June-July, 1979	Singh et al, 1981a
Los Angeles, CA	5 (average) p-xylene 6.5 (average) o-xylene 12 (average) m-xylene	September-November, 1967	Altshuller et al., 1971
Azusa, CA	2 (average) p-xylene 3 (average) o-xylene 5.5 (average) m-xylene	September-November, 1967	Altshuller et al., 1971
Chicago, IL	>1 all isomers	Indoor air of homes	Jarke et al., 1981
Los Angeles, CA	6 (average) p-xylene 16 (average) o-xylene 8 (average) m-xylene	1966	Lonneman et al., 1968
Los Angeles, CA	11-45 m-, p-xylene 4-13 o-xylene	Fall, 1981	Grosjean and Fung, 1984
Los Angeles, CA	10-35 m-, p-xylene 5-15 o-xylene	September-October, 1961	Altshuller and Bellar, 1963
Janesville, WI	0.6 m-, p-xylene 0.1 o-xylene	August, 1977 - background levels; levels near GM auto painting plant were up to 14 times greater	Sexton and Westberg, 1980
Newark, NJ	0.59 (mean) m-, p-xylene 0.26 (mean) o-xylene	Summer, 1981; concentrations in winter 1982 were up to 2 times higher	Harkov et al., 1984
Elizabeth, NJ	0.75 (mean) m-, p-xylene 0.22 (mean) o-xylene	Summer, 1981; concentrations in winter 1982 were up to 2 times higher	Harkov et al., 1984

TABLE 3-3 (cont.)

Sampling Location	Concentration (ppb)	Sampling Dates/Remarks	Reference
Camden, NJ	0.49 (mean) m-, p-xylene 0.15 (mean) o-xylene	Summer, 1981; concentrations in winter 1982 were up to 2 times higher	Harkov et al., 1984
Six New Jersey cities	3.21 (average) m-, p-xylene 1.15 (average) o-xylene	1979 (entire year)	Harkov et al., 1981
Rural North Carolina	0.7 (median) m-, p-xylene 0.35 (median) o-xylene	September, 1981-October, 1982	Sella et al., 1984
Houston, TX	2.1-3.4 p-xylene 5.4-7.8 m-xylene 3.0-4.8 o-xylene	NR	Bertsch et al., 1974
Hamilton, OH	30-48 (all isomers)	downwind of a hazardous waste remedial action site	Levine et al., 1985
Houston, TX	3.84 (mean) m-, p-xylene 1.30 (mean) o-xylene	May, 1980	Singh et al., 1981b
St. Louis, MO	0.95 (mean) m-, p-xylene 0.31 (mean) o-xylene	May-June, 1980	Singh et al., 1981b
Denver, CO	2.86 (mean) m-, p-xylene 1.28 (mean) o-xylene	June, 1980	Singh et al., 1981b
Riverside, CA	2.23 (mean) m-, p-xylene 1.10 (mean) o-xylene	July, 1980	Singh et al., 1981b
Five California cities	7-32 o-xylene 23-95 m-, p-xylene	NR	Neligan et al., 1965

Singh et al. (1981a) calculated average daily inhalation doses for xylenes based on an average air intake of 23 m^3 at 25°C and 1 atm for a 70 kg human; the daily doses were calculated by linear interpolation between measured field data. For example, in Los Angeles, a mean atmospheric o-xylene concentration of 1.93 ppb corresponded to an average inhalation dose of 192 µg/day.

Automobile exhaust is considered the major emission source of xylene to the atmosphere with annual U.S. emissions approaching 1.1 billion pounds (Singh et al., 1981a). The average hydrocarbon composition of automobile exhaust contains 6.5% m- and p-xylene and 2.5% o-xylene (Nelson and Quigley, 1984). The global release of xylenes from vehicular combustion has been estimated at 0.5-1.0 million tons (Fishbein, 1985). Xylene emissions to the atmosphere also result from its production and use as a chemical intermediate, from gasoline blending and distribution, from mold and core decomposition in iron foundries, from evaporation in solvent applications (degreasing, textiles, adhesives, paints) and from emissions from forest fires (Weant and McCormick, 1984). Coal pyrolysis is also an emission source of xylene (Felder and Gilman, 1984).

The sampling of indoor as well as outdoor environments has shown that indoor xylene concentrations can exceed those found outdoors. Seifert and Abraham (1982) compared the levels of m- and p-xylene measured in apartments, a conference room, a casino and outdoors next to dewellings. Concentration ranges of 4-10 and 2-11 ppb of m- and p-xylene, respectively, were reported for kitchens and other rooms. The xylene range outdoors was 0.9-7 ppb. Fishbein (1985) has attributed higher indoor pollutant levels to agents in construction materials and consumer products and pollutants introduced as a consequence of cooking, fuel burning and tobacco smoke.

3.4. DERMAL

Pertinent data regarding dermal exposure to xylenes could not be located in the available literature as cited in the Appendix. Dermal exposure is possible during gasoline handling and while using xylene solvents.

3.5. SUMMARY

Xylenes have been detected in drinking waters, groundwaters, surface waters, leachates and industrial effluents (see Table 3-1). The U.S. EPA's Groundwater Supply Survey detected xylene in ~2% of 945 finished water supplies using groundwater sources throughout the United States (Westrick et al., 1984). The sources of xylene exposure to natural waters include leaching from waste dumps and contaminated soil, industrial effluents and removal of xylene from the atmosphere by rainfall. Xylene has been detected in human breast milk (Pellizzari et al., 1982) and coffee (Wang et al., 1983). Xylene has been detected in ambient atmospheres throughout the United States (see Table 3-3) and the world. Automobile exhaust is considered the major emission source of xylene to the atmosphere (Singh et al., 1981a). Other sources of xylene emission to air include its production and use as an intermediate, gasoline blending and distribution, decomposition product in iron foundries, evaporation during solvent applications, forest fires and coal pyrolysis (Weant and McCormick, 1984; Felder and Gilman, 1984).

4. PHARMACOKINETICS

Where possible, the specific isomers of xylene will be noted; otherwise, "xylene" may refer to a mixture of the isomers or an unspecified isomer.

4.1. ABSORPTION

The available studies on xylene absorption in man are concerned primarily with inhalation and dermal exposure since these routes are occupationally important. Astrand et al. (1978) reported a study on 12 male volunteers who were exposed by inhalation to mixed xylene (49.4% m-xylene, 8.8% o-xylene, 1.4% p-xylene and 40.4% ethylbenzene) through a breathing valve. Each subject was exposed for four 30-minute periods; one period at rest and three on a bicycle ergometer. Six men were exposed at 870 mg/m^3 (200 ppm) xylene for 30 minutes of rest followed by 90 minutes (3x30 minutes) at a work load of 50 W. The remaining six men were exposed at 435 mg/m^3 (100 ppm) xylene for 30 minutes at rest, followed by 30 minutes at each increasing work load of 50, 100 and 150 W. Heartbeat and ventilatory rate and volume were monitored. At rest and during light work (50 W), pulmonary uptake of xylene was ~63% over the 2-hour exposure period. More strenuous exercise caused an increase in the relative amount of xylene taken up, but correction for increased pulmonary exchange showed that uptake efficiency gradually decreased from 63-64% at rest and 50 W exercise to 51% at 150 W exercise.

Six male volunteers were exposed to m-xylene (laboratory grade) at 3.9 mmol/m^3 (414 mg/m^3 or ~100 ppm) for 6 hours/day on 5 consecutive days and tested for xylene uptake (Riihimaki et al., 1979a). The final 3 hours of exposure on the fifth day was at 8.2 mmol/m^3 (870 mg/m^3 or 200 ppm).

These subjects were exposed at rest in a chamber so that uptake was actually by inhalation and percutaneous absorption. Absorption of xylene ranged from 54-68%, averaging ~60%, and remained relatively constant throughout the exposure period. In a similar study, Riihimaki et al. (1979b) exposed 16 male volunteers to m-xylene in combination with exercise. Exposure was 6 hours daily (3 hours in morning, 1 hour with no exposure, 3 hours afternoon exposure) on 5 successive days for 2 weeks. One group (n=8) was exposed to ~90 ppm (390 mg/m^3) m-xylene on the first 4 days and 3 hours on the fifth day with m-xylene at 191 ppm (830 mg/m^3) for the final 3 hours of each week, and exercised on a bicycle ergometer (100 W) for four 10-minute periods each day. A second group of volunteers (n=8) was exposed to 70 ppm (304 mg/m^3) with peak levels of 200 ppm (868 mg/m^3) every hour during the morning and afternoon exposures. The peak concentrations lasted 10 minutes and 5 minutes was allowed for the rise and fall of m-xylene concentrations in the chamber. A 10-minute work period (100 W) coincided with each of the peak exposure periods (four/day). On the afternoon (3 hours) of the fifth day, exposure was at 130 ppm (565 mg/m^3) with two peak m-xylene concentrations at 400 ppm (1736 mg/m^3). Absorption of m-xylene measured as the difference between the chamber air concentration and the exhaled air concentration was ~60% under all test conditions. At rest, absorption ranged from 53-68%, while during exercise absorption was consistently similar (55-71%).

Consistent with the absorption factors reported by Riihimaki et al. (1979a,b), Sedivec and Flek (1974, 1976) reported that humans exposed by inhalation to o-, m-, p-xylene or a mixture (1:1:1) of the three absorbed ~64%. In 15 experiments, four persons each, were exposed for 8 hours at 200 or 400 mg/m^3 (45 or 90 ppm). All isomers or the mixture were absorbed almost identically; different exposure levels or exposure at different periods during the 8 hours did not affect absorption. Individual differences did occur between subjects and appeared to be indirectly related to ventilation rate (decreased retention with increased ventilation).

In a study in which 15 male volunteers were exposed to mixed xylene at 435 and 1300 mg/m³ during rest and 1300 mg/m³ while exercising (100 W), Gamberale et al. (1978) reported mean absorption levels of 180, 541 and 1210 mg/70 minutes of exposure, respectively. Assuming a daily ventilatory volume of 20 m³ while at rest and 10 m³/8 hours while performing work, absorption efficiency was ~43, 43 and 64%, respectively. These values are corroborative with those reported by Riihimaki et al. (1979a,b) and Sedivec and Flek (1974, 1976).

Senczuk and Orlowski (1978) conducted laboratory tests with five men and five women exposed to 100, 300 and 600 mg m-xylene/m³ (23, 69 and 138 ppm) for 8 hours at rest with two 30-minute breaks. The average ventilation rates were 0.458 m³/hour for women and 0.575 m³/hour for men. The average amounts of m-xylene absorbed by women during 8 hours of exposure at 100, 300 and 600 mg/m³ were 272, 724 and 1359 mg, so that pulmonary retentions were 74, 66 and 62%, respectively. In men, the absorbed doses were 342, 909 and 1711 mg and the respective absorption coefficients were 74, 66 and 62%. Senczuk and Orlowski (1978) noted that retention was quite high initially but decreased throughout the exposure period.

Percutaneous absorption of xylenes in man is quite low (Riihimaki and Pfaffli, 1978; Engstrom et al., 1977; Riihimaki, 1979a; Dutkiewicz and Tyras, 1968) compared with pulmonary absorption. Riihimaki and Pfaffli (1978) exposed five male volunteers wearing full face respirators to 300 or 600 ppm (1300 or 2600 mg/m³) for 3.5 hours. For comparison, the subjects were also exposed without respirators to xylene at 20 ppm (87 mg/m³) for 3.5 hours. Amounts of xylene absorbed (determined by the amount excreted in urine and expired air) after percutaneous exposure at 300 and 600 ppm and inhalation exposure at 20 ppm were 21, 45 and 38 mg, respectively. Based on an assumption of 60% pulmonary absorption, these authors concluded that percutaneous absorption represented 1.3-1.4% of the xylene that would have been absorbed by the lungs at the same exposure levels. Based on the average skin surface area of the subjects (1.88 m²), percutaneous absorption was 0.32 µg/cm²/hour for 300 ppm exposure and 0.68 µg/cm²/hour for exposure to 600 ppm m-xylene vapor.

Absorption of pure liquid m-xylene through the hands was studied by Engstrom et al. (1977) and Riihimaki (1979a). Subjects immersed both hands in pure (laboratory grade) m-xylene for 15 minutes and precautions were taken to minimize inhalation exposure. Absorbed xylene was determined to be that quantity excreted in the urine as methyl-hippuric acid within 22 hours after exposure. Riihimaki (1979a) reported that ~22.5 mg of m-xylene was absorbed within 15 minutes and the average area of the hands was near 900 cm² for both hands. The absorption rate was, therefore, near 100 µg/cm²/hour. Engstrom et al. (1977) had estimated previously that ~35 mg of m-xylene was absorbed during a 15-minute exposure and the absorption rate was ~120 µg/cm²/hour. This extreme dermal exposure was equated to an inhalation exposure at 100 ppm (434 mg/m³) of equal duration.

Dutkiewicz and Tyras (1968) reported that dermal absorption of pure xylenes through the skin of the forearm was 4.6-9.6 mg/cm²/hour. Ten volunteers had liquid xylene applied to the forearm under a sealed watch-glass for 1 hour. The xylene absorbed through the skin was that amount not recovered after several ethanol washings of the skin. Compared with lower levels determined in other studies (Riihimaki and Pfaffli, 1978; Riihimaki, 1979a), this higher rate of absorption reported may be due to evaporative loss, loss during washing or the absorptive difference between the hands (thick skin) and the forearm (thin skin).

Absorption of xylene from the gastrointestinal tract was nearly complete in rabbits orally dosed with 1.5-2.0 mℓ of o-, m- or p-xylene; 85-90% of the administered dose was accounted for as metabolites in the urine collected for 3 days after dosing (Bray et al., 1949). Pulmonary excretion may have accounted for the remaining xylene (Sections 4.3. and 4.4.).

4.2. DISTRIBUTION

Using whole-body autoradiography to detect radiolabeled xylene and metabolites, Bergman (1978) reported distribution of the compound in many tissues and organs of exposed mice. ^{14}C-m-xylene was administered to mice by inhalation for 10 minutes and the mice were embedded, frozen and sectioned before exposure to X-ray film. In mice sacrificed immediately after xylene exposure, radiolabel was detected in the lungs, liver and kidneys. Rapid distribution to the brain and adipose tissue was also evident. Two hours after exposure, radiolabel was restricted to the bronchi of the lungs and the intestine. The last traces of xylene were detected in the adipose tissue of mice sacrificed 4 hours after exposure (Bergman, 1978).

Nawrot et al. (1980) reported in an abstract that in CD-1 mice treated by gavage (dose not specified) on gestation day 12 or 15, maximal distribution of ^{14}C-m-xylene to the liver occurred 2 hours after exposure. Radioactivity, reportedly from metabolites of m-xylene, was detected in fetal tissues, maximally 2 hours after dosing.

In rats exposed to ^{14}C-p-xylene for 1-8 hours by inhalation at 208 mg/m^3 (48 ppm), radiolabel was detected (in decreasing concentration) in the kidneys, subcutaneous fat, sciatic nerve, blood, liver, lungs, spleen, muscles, cerebrum and cerebellum (Carlsson, 1981). Levels in subcutaneous fat increased with time: 182 nmol equivalents/g at 4 hours and 270 nmol/g at 8 hours. Levels in kidney were high (700 nmol equivalents/g) throughout the entire exposure period. Half-life for ^{14}C disappearance from subcutaneous fat was 2.2 hours following 1 hour of exposure and 6.9 hours after 8 hours of exposure. Following an 8-hour exposure period, metabolites accounted for 50, 60 and 18% of the radioactivity in the liver, blood and cerebrum, respectively. Distribution to all tissues was rapid, with near maximal levels attained in tissues (except in kidneys and subcutaneous fat) within 1 hour.

Data available on the accumulation of xylene indicate that the adipose tissue is the predominant site of retention in laboratory animals and humans. The xylene accumulated in the adipose tissue, however, may represent only ~5-10% of the total absorbed dose (Engstrom and Riihimaki, 1979). Unreacted xylene is found in the subcutaneous fat of rats exposed to xylene by inhalation (Carlsson, 1981). Xylene was also found in the kidney (4-5 times greater than in the subcutaneous fat) during exposure, but levels decreased after exposure was terminated. Xylene accumulates in the perirenal fat (Savolainen et al., 1978; Savolainen and Pfaffli, 1980) as well as brain tissue (Savolainen and Pfaffli, 1980). When rats were exposed to xylene subchronically (5-18 weeks), xylene accumulation in the perirenal fat reached a maximum by week 5 and decreased thereafter.

Few data regarding the distribution of xylene in humans are available. Riihimaki et al. (1979a) noted that xylene, distributed by the blood, is predominantly associated with serum proteins (90%) and only a small fraction (10-15%) exists in the serum. Engstrom and Riihimaki (1979) studied the distribution of m-xylene to the subcutaneous fat in 18 male volunteers exposed to 64-400 ppm (278-1740 mg/m³) xylene for 6 hours/day for up to 6 days. Subcutaneous biopsies of gluteal adipose tissue were taken for xylene determination. This study showed that distribution and accumulation of xylene did occur in the adipose tissue.

The accumulation of mixed xylene in humans was studied in 12 male volunteers exposed to 100 or 200 ppm (435 or 870 mg/m³) by inhalation for 2 hours (Engstrom and Bjurstrom, 1978). Six subjects were exposed to 200 ppm (868 mg/m³) mixed xylene (49.4, 8.8 and 1.4%, m-, o- and p-xylene and 40.4% ethylbenzene) for 30 minutes at rest and for 90 minutes exercising at 50 W of work. A second group of six subjects was exposed at 100 ppm (434 mg/m³) for four 30-minute intervals of rest and work at 50, 100 and 150 W, respectively. In both groups, exposure was interrupted for 20 minutes after the initial rest period before exercise. Adipose tissue biopsies from the subcutaneous layer in the gluteal area were taken 0.5, 2, 4 and 22 hours after the termination of exposure. The uptake and accumulation of xylene was proportionately related to the amount of body fat of the subjects. The concentration of m-xylene, p-xylene and ethylbenzene (o-xylene could not be separated in the chromatographic column used) in adipose tissue was dose-dependent. In subjects exposed to 200 ppm, mean tissue levels were 8, 9, 6 and 6 mg/kg after 0.5, 2, 4 and 22 hours, while levels in subjects exposed to 100 ppm were 4, 6, 4 and 8 mg/kg, respectively. The authors (Engstrom and Bjurstrom, 1978) noted that the 4-hour values were based on only four subjects and should be viewed with caution. Since there was no significant change in the concentration of xylenes in adipose tissue from 2-22 hours postexposure, the elimination of the solvent from this tissue was regarded as slow, and accumulation after repeated exposure is possible.

In a subsequent study, Engstrom and Riihimaki (1979) exposed 18 male volunteers to 64-400 ppm (278-1740 mg/m³) m-xylene by inhalation on various daily exposure schedules for 6 days. Three different exposure patterns were used. Exercise (bicycle ergometer) coincided with peak levels of exposure (up to 400 ppm) in the first. The second included constant xylene concentrations with exercise, while the third pattern used varied exposure levels without exercise. The uptake of m-xylene to adipose tissue was greatest in subjects who were exercising during high levels of exposure (8.0% of total absorbed dose; 20.6 mg/kg fat), while exercise at constant exposure levels caused moderate uptake (7.5%; 17.7 mg/kg fat). Subjects exposed while at rest showed the least uptake of xylene in the adipose tissue (3.7%; 9.5 mg/kg fat). The half-lives of m-xylene in the adipose tissue were 77.5, 47.5 and 49.5 hours, respectively, for the three dose schedules. It is important to emphasize that exposure to m-xylene at ~100 ppm (TLV level) for 6 hours/day, simulating occupational exposure, results in the retention of xylene in adipose tissue and the half-life was 47.5 hours, so that daily and week-to-week accumulation is possible. Corroboratively, Riihimaki et al. (1979a) cited a distribution coefficient for xylene between adipose tissue and blood of 97:1 and suggested a persistence time of ~67 hours for this tissue.

4.3. METABOLISM

The three isomers of xylene (o-, m- and p-xylene) are metabolized by slightly different pathways, which results in different proportions of metabolites. Generally 85-95% of the absorbed xylene is metabolized and excreted in the urine. Only a small amount (5-10%) is unmetabolized and exhaled through the lungs. Metabolism of the xylenes in laboratory animals is somewhat different from that in humans.

The urinary metabolites of o-, m- and p-xylene following oral administration (in olive oil) were determined in rats, guinea pigs and rabbits (Fabre et al., 1960). Animals were treated by gavage at 40 mg/kg/day for 1 week. Toluic acid was a urinary metabolite following treatment with all isomers. Additionally, animals ingesting o-xylene excreted 3,4-dimethylphenol and those receiving p-xylene excreted 2,5-dimethylphenol and unchanged p-xylene. Quantitative data on the urinary metabolites in each of the species tested were not available, but the metabolites identified from all three species were comparable.

Laham (1970) reported in a brief summary of earlier studies with rats, rabbits and guinea pigs that all xylene isomers are oxidized to toluic acid, which is then conjugated with glycine (methylhippuric acid). The respective isomers of toluylglucuronic acid were reported after exposure to all three isomers, but the percentages of these toluic acid conjugates in contrast to methylhippuric acid were not reported. Aromatic hydroxylation occurs to a lesser extent to produce isomeric xylenols. The xylenols identified following o- and p-xylene exposure were 3,4- and 2,5-xylenol, respectively. m-Xylene could theoretically be metabolized to three isomeric xylenols, but none were detected. The xylenols are conjugated and excreted as glucuronides or sulfate esters. Specific exposure details were not reported.

Bakke and Scheline (1970) also reported phenolic metabolites (aromatic hydroxylation) of o-, m- and p-xylene following oral administration in rats. Male albino rats were maintained on a neomycin sulfate-containing diet for 7 days, while "control" urine samples were taken to determine background urinary phenols. On the 7th day, three rats each were treated by gavage with o-, m- or p-xylene at 100 mg/kg in propylene glycol. Urine samples collected over the subsequent 48 hours were analyzed by gas chromatography and compared with standards. Phenolic metabolites of o-xylene were 3,4-dimethylphenol (0.1% of administered dose) and 2,3-dimethylphenol (0.03%), while 2,4-dimethylphenol (0.9%) and 2,5-diemthylphenol (1.0%), respectively, were identified following m- and p-xylene treatment. These results indicated that there is a minor metabolic pathway involving ring hydroxylation that accounts for 1% or less of the dose. With o-xylene, but not with m- or p-xylene, a small but unquantified amount of methylbenzyl alcohol was found in the rat urine.

The metabolism of m- and o-xylene to phenolic metabolites was studied in male Wistar rats treated orally with 0.9 g/kg (Mikulski et al., 1979a). Blood and urinary phenols were determined at intervals from 0.5-36 hours after treatment. Maximal blood phenol levels of ~8 and 13 μg/mℓ for m- and o-xylene, respectively, were reached within the first half-hour of the study. Urinary phenol excretion was greatest at 9 hours after treatment and reached rates <0.1 mg/hour. For m- and o-xylene, urinary excretion of phenol represented 0.8 and 0.7% of the administered dose, respectively.

The metabolic pathway of xylene to mercapturic acid in the rat was studied by Van Doorn et al. (1981). The thioether conjugates represent 2.4 and 1.3% of the administered dose (106 mg/kg intraperitoneally) of m- and p-xylene, respectively, but accounted for 16% of the o-xylene administered to rats. The metabolism of o-xylene to o-methylbenzylmercapturic acid entails initial oxidation to o-methylbenzyl alcohol, sulfation and finally conjugation of o-methylbenzyl sulfate with glutathione. Van Doorn et al. (1980) reported that liver glutathione levels were decreased to 26% of pretreatment levels after o-xylene treatment. Van Doorn et al. (1981) noted that o-methylbenzyl sulfate in vitro was ~20 times more reactive in combining with glutathione than were m- or p-methylbenzyl sulfate. This apparently would lead to higher levels of o-methylbenzylmercapturic acid compared with that for the m- and p-isomers. N-acetyl-S-(O-methylbenzyl) L-cysteine was identified in rat urine after administration of o-xylene.

The profile of metabolites of m-xylene has been found to be dose-dependent. Ogata and Fujii (1979) reported that urinary excretion of m-methylhippuric acid (glycine conjugate of m-toluic acid) accounted for 74.8, 65.4 and 53.5% of the m-xylene administered subcutaneously at 87, 174 and 348 mg/kg, respectively, in male Wistar rats.

Consistent with metabolism data reported by Van Doorn et al. (1981) in the rat, Bray et al. (1949, 1950) noted that o-xylene was metabolized in a manner different from m- or p-xylene in rabbits. Rabbits were treated orally with o-xylene at 0.9, 1.35 or 1.8 g/rabbit, m-xylene at 1.74 g/rabbit, and p-xylene at 1.7 g/rabbit. Urine was collected for 3 days postexposure. The urinary metabolites expressed as percent of administered dose for the three xylene isomers are summarized in Table 4-1. o-Xylene is readily oxidized and conjugated to the glucuronide of toluic acid. About 30% of the administered o-xylene is metabolized to this product, while 2 and 1% of the m- and p-xylene are excreted in this form. The m- and p-isomers are predominantly excreted as their respective methylhippuric acid metabolites. Aromatic hydroxylation to dimethylphenol occurs to a small degree for all isomers administered to rabbits (Bray et al., 1950).

Carlone and Fouts (1974) and Smith et al. (1982) studied the metabolism of p-xylene by rabbit liver and lung in vitro. Carlone and Fouts (1974) used liver and lung microsomal enzyme preparations to determine the metabolism of p-xylene and found the major metabolite to be p-toluic acid. The rate of toluic acid formation by lung microsomes plus lung soluble fraction was about half the rate for liver microsomes plus liver soluble fraction.

TABLE 4-1

Urinary Metabolites of o-, m- and p-Xylene in Rabbits[a]

Xylene	Oral Dose (g/rabbit)	Percent of Administered Dose[b] Methyl-hippuric Acid[c]	Toluyl Glucuronide[d]	Mercapturic Acid[e]	Dimethyl-phenol
o-Xylene	0.90	30	22	NR	NR
	1.35	36	29	8	2
	1.80	22	32	6	NR
m-Xylene	1.74	79	2	4	4
p-Xylene	1.70	87	1	0	2

[a] Source: Bray et al., 1949, 1950

[b] Collected over 3 days postexposure

[c] Isolated as "ether-soluble acid"

[d] Isolated as "ester glucuronide"

[e] Isolated as "ethereal glucuronide sulfate"

NR = Not reported

The rate of toluic acid formation by lung microsomes plus liver soluble fraction was, however, about twice that for liver microsomes and soluble fraction. Based on the following metabolic scheme

$$\text{p-xylene} \xrightarrow[\text{oxidation}]{\text{microsomal}} \underset{\text{alcohol}}{\text{p-methylbenzyl}} \xrightarrow[\text{dehydrogenase}]{\text{alcohol}} \text{p-methyl benzaldehyde}$$

$$\underset{\text{(p-tolualdehyde)}}{\text{p-methyl benzaldehyde}} \xrightarrow[\text{oxidase}]{\text{aldehyde}} \underset{\text{(toluic acid)}}{\text{p-methylbenzoic acid}}$$

the authors speculated that the lung soluble fraction lacked sufficient alcohol dehydrogenase or aldehyde oxidase. This was not entirely the case since lung microsomes incubated with p-xylene in the presence of these two enzymes showed little increase in metabolic rate to toluic acid (Carlone and Fouts, 1974).

Smith et al. (1982) used whole, perfused livers and lungs of rabbits to study the metabolism of p-xylene. The major hepatic metabolite was n-p-toluylglycine (p-methylhippuric acid), which represented 69% of the perfused dose. Unconjugated p-toluic acid represented ~4.5% and p-methylbenzyl alcohol represented ~0.02% of the perfused p-xylene (~20% of the perfused p-xylene was lost through evaporation). Perfusion of p-xylene into the isolated lungs resulted in 32.1, 6.2 and 0.9% of the dose as p-methylbenzyl alcohol, p-toluic acid and 2,5-dimethylphenol, respectively. No glycine conjugate of toluic acid was recovered from the lung. About 15% of the perfused p-xylene was recovered unchanged in the perfusate and ~46% was exhaled from the lung. These data are consistent with those reported by Carlone and Fouts (1974), indicating that microsomal oxidation occurs primarily in lung tissue. The initial oxidation of p-xylene proceeded more rapidly in the lung (328 nmol/min/g tissue) than liver (73 nmol/min/g tissue), but overall the liver had a greater capacity for p-xylene removal from the circulation and subsequent metabolism.

With rat liver enzymes in vitro, the Michaelis' constants (K_m) for conjugation of m-, o- and p-toluic acid with glycine to form their respective methylhippuric acids were 3.7×10^{-4}, 2.7×10^{-3} and 5.2×10^{-4} M (Mikulski et al., 1979b). These data indicate the decreased affinity of the rat liver enzyme for o-toluic acid, which may contribute to o-toluic acid being conjugated alternately with glutathione.

Ogata et al. (1979) compared the metabolism of o-xylene in female rats with that in human volunteers. Female Wistar rats treated with 1.2 g o-xylene/kg (intraperitoneally) excreted predominantly o-toluic and glucuronide (56.6%), and less o-methylhippuric acid (15.9%). In humans ingesting 39 or 78 mg/kg of o-xylene (single oral dose), the major urinary metabolite was o-methylhippuric acid (MHA) (33-36%), and o-toluic acid glucuronide (TAG) represented ~1.3% of the administered dose. In volunteers exposed by inhalation (138 ppm or 600 mg/m³ o-xylene for 3 hours), similar proportions of metabolites were recovered after oral dosing of humans (Ogata et al., 1980). In humans, 33.1% was excreted as o-MHA and 1.0% as o-TAG after oral dosing; after inhalation, 46.4% was excreted as o-MHA and only a trace as o-TAG.

In humans, m-xylene is predominantly metabolized to m-methylhippuric acid (m-toluic acid) (Riihimaki et al., 1979a,b). The urinary excretion of metabolites of m-xylene was studied in male volunteers exposed by inhalation. Although several exposure schedules were used by these authors (see Section 4.1.), excretion of urinary metabolites was studied only after the first day's exposure (~100 ppm for 6 hours). m-Methylhippuric acid accounted for ~84% of the absorbed m-xylene within 24 hours postexposure.

2,4-Xylenol (2,4-dimethylphenol) accounted for 1-2% and excretion of m-xylene in the expired air accounted for ~4%. An additional 16.7-21.3% of the administered dose was collected as urinary m-methylhippuric acid 2-6 days postexposure.

In several experiments using four male volunteers (aged 28-50), the purified xylene isomers were administered separately at 200 and 400 mg/m^3 (870 and 1740 ppm) for 8 hours and urinary metabolites were measured during exposure and for 40 hours postexposure (Sedivec and Flek, 1976). At the two concentrations tested, the retention was almost the same for all isomers (62.4-64.3%) and did not vary with duration of exposure. After exposure, the exhaled xylene followed a multiphasic pattern of decrease with a rapid initial rate. The total amount exhaled over 48 hours was equivalent to 3.5, 5.8 and 5.3% of the retained dose of p-, m- and o-xylene, respectively. No free toluic acid metabolites were discovered in the urine. Conjugated urinary metabolites were restricted to toluic acids bound to glycine (methylhippuric acids) for all isomers. Based on data in rabbits (Bray et al., 1949), Sedivec and Flek (1976) suggested that at high dose levels of xylene, glycine may be depleted and glucuronide conjugation could occur as an "emergency" (substrate saturation) mechanism. Minor phenolic metabolites identified in the urine after administration of o-, m- or p-xylene were 2,3- and 3,5-xylenol, 2,4-xylenol or 2,5-xylenol, respectively.

Because of the relatively complete and consistent metabolism of xylenes to methylhippuric acids in humans, urinary methylhippuric acid has been used as a biological monitoring tool of occupational exposure to xylenes (Engstrom et al., 1976; Sedivec and Flek, 1976; Ogata and Hobara, 1979; Sugihara, 1979; Ogata et al., 1980). Urinary methylhippuric acid was excreted at a level proportional to xylene exposure. Because of the relatively low occurrence of methylhippuric acid in unexposed humans, this parameter may be used to estimate xylene exposure.

Engstrom et al. (1984) exposed four male human subjects to 150 ppm (655 mg/m^3) m-xylene for 4 hours. Approximately 97% and 2.5% of the urinary metabolites were m-methylhippuric acid and 2,4-dimethylphenol, respectively, and 0.05% was methylbenzyl alcohol. Thus, m-xylene was metabolized primarily by oxidation of the side chains, while ring oxidation was of minor importance.

4.4. EXCRETION

Excretion of the xylenes in laboratory animals and humans is predominantly by urinary elimination of metabolites, but pulmonary exhalation of unchanged solvent does account for ~5% of the absorbed dose (Sedivec and Flek, 1976; Astrand et al., 1978). In animals and humans the major urinary metabolites (80-90% of administered dose) of m- and p-xylene are the corresponding glycine conjugates of toluic acid (see Section 4.3.). In animals, o-xylene is metabolized in nearly equal amounts to o-toluyl glucuronide and o-methylhippuric acid, while urinary excretion of the glucuronide conjugate represents a minor fraction (1-2%) of administered o- and m-xylene isomers. In humans, all isomers appear to be metabolized similarly and excreted almost entirely as methylhippuric acid (Sedivec and Flek, 1976).

Minor metabolites identified in the urine of animals treated with the xylene isomers included mercapturic acid, unconjugated toluic acid and dimethylphenol. o-Xylene may be more readily metabolized to its thioester conjugate (o-methylbenzylmercapturic acid) than the m- or p-isomer. The production of various isomers of dimethylphenol by aromatic ring hydroxylation represents only 1-4% of the administered dose in animals or humans.

Mercapturic acid has been reported as a minor metabolite in rabbits treated with all of the xylene isomers (Bray et al., 1949, 1950).

The rate of excretion of o-, m- and p-methylhippuric acid was studied in men exposed by inhalation to ~400 mg/m³ for 8 hours. Urine samples were taken every 2 hours for 14 hours (including exposure period) and at 8-hour intervals for up to 48 hours after the start of exposure. Excretion of the methylhippuric acid metabolites rose quite rapidly during exposure, reaching a mean level of ~135 mg during the first 2 hours of exposure and a maximum level of ~260 mg during the final 2 hours of exposure. After exposure was terminated, excretion decreased very rapidly to <50 mg for 4-6 hours postexposure. Throughout the remaining postexposure interval, low levels of methylhippuric acid continued to be excreted. To confirm the speculation that exposure to technical xylene would be similar, Sedivec and Flek (1976) also exposed volunteers to a 1:1:1 mixture of the xylene isomers. Overall, the rate of excretion followed a pattern similar to that seen with the purified isomers. When urinary methylhippuric acids were identified as to isomer, it was apparent that during the first 2 hours of exposure p-methylhippuric acid predominated (41.5%), and the o-methylhippuric acid level was less (23.8%) than expected. In later urine samples, each isomeric component approached the expected 33% of the total methylhippuric acid content.

The rate of urinary excretion of m-xylene metabolites in humans was studied in male and female volunteers exposed by inhalation at 100, 300 or 600 mg/m³ (23, 69 or 138 ppm) for 8 hours (Senczuk and Orlowski, 1978). During the first 4 hours of exposure, the rate of urinary m-methylhippuric acid excretion increased rapidly (to ~140 mg/hour for men exposed at 300 mg/m³). Excretion of m-methylhippuric acid continued to increase, though less dramatically, from 4 hours until exposure was terminated (maximum excretion rate of ~160 mg/hour for men exposed at 300 mg/m³). The maximum rates of m-methylhippuric acid excretion in men exposed at 100 and 600 mg/m³ were ~75 and 350 mg/hour, respectively. Maximum excretion rates were reached by the end of the exposure period. After exposure was terminated, the rate of m-methylhippuric acid excretion decreased rapidly to near zero by 30 hours. The rate of excretion during the exposure period was dependent on the absorbed dose of m-xylene. Based on these excretion studies, Senczuk and Orlowski (1978) suggested that m-xylene does not accumulate in the body (or, if so, to a very small extent) on a day-to-day basis after 8 hours of exposure at the levels tested.

The kinetics of excretion of urinary m-xylene metabolites were studied by Riihimaki et al. (1979a) using a group of six male volunteers exposed by inhalation at 414 mg/m³ for 4.5 days (6 hours/day) followed by a 3-hour exposure at 870 mg/m³ on the 5th day (see Section 4.3.). The rate of methylhippuric acid rose rapidly during exposure, dropping slightly during a 1-hour lunch break, and reaching a maximum at ~1.5 mmol/hour (equivalent to ~160 mg m-xylene/hour) within 2 hours postexposure. Elimination following exposure was characterized by two phases, the first rapid phase having a half-time of 1-2 hours and the second halved in ~10 hours. A third elimination phase having a half-time of ~20 hours was evident after the 5th day of exposure and was considered indicative of mobilization and elimination of cumulated xylene from the tissues. This third slow phase of elimination was more pronounced when exercise coincided with exposure and m-xylene uptake was elevated. Accumulation of m-xylene, therefore, appeared greater (Riihimaki et al., 1979b). The rate of pulmonary elimination of m-xylene was described as a two-phase process. The first phase was rapid, with half-times of 0.5-1.0 hours, and the second slower, with half-times of ~20 hours (Riihimaki et al., 1979a,b).

In male volunteers exposed by inhalation to 870 mg/m³ during rest and exercise at 50 W (series I) or at 435 mg/m³ during rest and exercise at 50, 100 and 150 W (series II) for 2 hours, pulmonary elimination of unchanged xylene (xylene isomers and ethylbenzene) was greatest immediately after exposure (see Section 4.3.) (Astrand et al., 1978). Subjects exposed in series I (mean total absorbed xylene, 1379 mg) expired 51, 16 and 3 mg xylene, respectively, by 4, 19 and 48 hours postexposure. In series II (mean total absorbed xylene 991 mg), subjects expired 29, 10 and 2 mg, respectively, by 4, 19 and 48 hours after the 2 hours of inhalation exposure. Total pulmonary elimination accounted for 5 and 4% of the absorbed solvent in series I and II, respectively.

Riihimaki and Pfaffli (1978) reported that elimination of m-xylene in the exhaled air following percutaneous exposure (3.5 hours) to vapor at 600 ppm (2600 mg/m³) (~44.5 mg m-xylene absorbed) was ~8 mg/m³ during the exposure period. Pulmonary excretion rate following inhalatory exposure at 20 ppm (87 mg/m³) for 3.5 hours (~37.9 mg m-xylene absorbed) was comparable. The kinetics of urinary excretion of m-methylhippuric acid following percutaneous (600 ppm) or inhalation (20 ppm) exposure was similar to that noted by Senczuk and Orlowski (1978). Initially, excretion was very rapid so that ~50% of the absorbed dose was excreted within the 35-hour exposure period. About 80% of the absorbed dose was excreted within 4 hours postexposure. After this period the excretion rate slowed somewhat but appeared complete within ~24 hours (Riihimaki and Pfaffli, 1978). The maximum excretion rate of m-methylhippuric acid in volunteers who immersed both hands in pure m-xylene for 15 minutes (~22.66 mg m-xylene absorbed) was ~5.3 mg/hour, occurring immediately after exposure was terminated (Riihimaki, 1979a).

Riihimaki (1979b) suggested that the conjugation of methylbenzoic acid with glycine forming methylhippuric acid was the rate-limiting step in xylene metabolism and elimination. This suggestion was based on excretion kinetics data obtained from one male volunteer treated orally and intravenously with methylbenzoic acid and methylhippuric acid, and also by analogy with toluene excretion. The rate of excretion of methylhippuric acid was notably slower when methylbenzoic acid was administered, necessitating glycine conjugation. The maximum rate of excretion approximated the maximum capacity of glycine conjugation (190 μmol/minute). The author further speculated that occupational exposure to xylene vapor at 780 ppm (3385 mg/m³) during light work or 270 ppm (1172 mg/m³) during moderate work for 8 hours/day (assuming 60% pulmonary absorption) would saturate the capacity of xylene metabolism. Possible hazardous accumulation of xylene or its metabolites may occur thereafter.

In an effort to determine a reliable method for estimating occupational xylene exposure, Engstrom et al. (1980) measured exposure levels of xylene and urinary methylhippuric acid, exhaled air and blood xylene levels of 15 painters. Breathing zone samples were taken on 3 consecutive days to determine daily TWA xylene levels. Following the exposure day, xylene levels in the blood and expired air and urinary methylhippuric acid were measured at various postexposure times and correlated to the TWA. TWA xylene levels were as high as 70 ppm (304 mg/m³). Exhaled air (r=0.63) and blood (r=0.75) xylene levels correlated poorly with different xylene exposures, while urinary methylhippuric acid (r=0.92) correlated quite well. Exposure to ~50 ppm (217 mg/m³) xylene (TWA) resulted in urinary methylhippuric acid levels of ~500 mg/g creatinine during the last 4-5 hours of the daily exposure. Engstroem et al. (1980) suggested that urinary methylhippuric acid may give a good estimate of occupational TWAs of xylene.

Engstrom et al. (1984) (see Section 4.3.) exposed four male human subjects by inhalation to 150 ppm (655 mg/m^3) m-xylene. Approximately 97% of the m-xylene was excreted as methylhippuric acid 24 hours after exposure.

4.5. ENZYME INDUCTION AND INHIBITION

Xylene isomers have been shown to be inducers of the cytochrome P-450 system by a number of investigators. Toftgard and Nilsen (1982) exposed male Sprague-Dawley rats by inhalation to 2000 ppm of a mixture of solvents (o-, 2%; m-, 64.5%; p-xylene, 10%; ethylbenzene, 23%; toluene, 0.5%; benzene, 0.2%) or to individual constituents. All solvents induced hepatic cytochrome P-450 content by ~75% with the exception of p-xylene (~40% induction). *In vitro* studies using hepatic microsomes from either uninduced (control) or solvent-induced rats showed that all solvents induced 7-ethoxyresorufin o-deethylase activity ~300-400% with the exception of p-xylene, which showed no induction and also increased hydroxylation of n-hexane and benzo(a)pyrene ~10-fold.

In kidney microsomes, an increased concentration of cytochrome P-450 was obtained following exposure to the solvent mixture or to o- or m-xylene. All solvents induced o-deethylation of 7-ethoxyresorufin 2- to 6-fold. The hydroxylation of n-hexane was only slightly induced by the mixture, ethylbenzene or o-xylene. In lung microsomes, all xylene isomers, but not ethylbenzene, caused a decrease in cytochrome P-450 content; however, o-deethylase activity was not affected.

Experiments using methodology similar to that described above were performed to show that hepatic induction can be detected at xylene concentrations as low as 75 ppm (6 hours/day for 3 days) and that xylene induces an isozyme very similar, if not identical, to that induced by phenobarbital (Toftgard, 1983; Toftgard and Nilsen, 1982; Toftgard et al., 1983a,b).

Additionally, the effects produced by the xylene mixture reflected the content of the dominating component m-xylene (Toftgard and Nilsen, 1982).

Similar results have been published by other investigators. Inhalation exposure of rats to xylene isomers induced cytochrome P-450 and associated enzymatic activities in hepatic and renal microsome (Elovaara, 1982; Pyykkö, 1980; Ungvary et al., 1980a), but not in lung microsomes (Pyykkö, 1980). Pathiratne et al. (1986) found that a mixture of xylenes injected intraperitoneally into male Sprague-Dawley rats at a concentration of 20 mM/kg/day for 3 days induced cytochrome P-450 isozymes similar to those induced by phenobarbital. The xylene mixture increased its own metabolism, as well as that of toluene and benzene when measured in an in vitro system.

Patel et al. (1978) investigated the effects of p-xylene administration on pulmonary and hepatic p-xylene hydrolase activities. Female Sprague-Dawley rats were administered p-xylene (1 g/kg) for 4 consecutive days by intraperitoneal injection or by gavage. Rats were also exposed to p-xylene vapors at 1000±49 ppm, 4 hours/day for 4 days. Exposure by all routes decreased pulmonary microsomal p-xylene hydroxylase activity ~65% of control values. Restoration of activity was gradual with ~85% of normal activity observed 8 days after termination of treatment. An identical inhibition recovery pattern was produced by a single intraperitoneal injection of p-xylene at 1 g/kg. Pretreatment of the rats with phenobarbital (1 mg/mℓ in the drinking water for 3 days) prevented the inhibition of pulmonary microsomal p-xylene hydroxylase. Hepatic p-xylene hydroxylase activity was not affected by the p-xylene treatments. Experiments in vitro showed that inactivation of cytochrome P-450 by p-xylene required the metabolic conversion of p-xylene to p-tolualdehyde. Because the lung cannot form p-tolualdehyde, the authors assumed that the inactivation of lung enzymes in vivo following exposure to p-xylene was due to the aldehyde intermediate, which was presumably formed in the liver.

Smith et al. (1982) performed perfusion studies with p-xylene in rabbit liver and lung. The major pulmonary metabolite was p-methylbenzyl alcohol, reflecting a deficiency of alcohol dehydrogenase in the lung. The principal metabolite in the liver perfusate was methylhippuric acid. No p-tolualdehyde was released from the perfused liver; however, small amounts of p-toluic acid were measured in the lung perfusate.

Riihimaki et al. (1982) studied the effect of ethanol administration on the metabolism of m-xylene. Fourteen subjects were used, 10 students aged 21-26 and 4 research assistants aged 30-38. It is not clear how the subjects were distributed among the experimental groups. Each of the designated xylene exposures took place in an inhalation exposure chamber for a single period of 4 hours. An interval of 1 week occurred between each of the exposures. When ethanol was administered, it was administered orally ~30 minutes before the start of the inhalation exposures. The experimental design was as follows:

Week	Xylene Exposure Group (mmol/m^3)			Ethanol (g/kg)
	A (n=5)	B (n=5)	C (n=4)	
1	7.7	5.9	11.9	--
2	5.9	5.9	11.9	0.8
3	--	--	--	0.8
4	10.7	11.5		--
5	11.9	11.9		0.8

In groups A and B blood samples were analyzed both during and 1-hour postexposure for m-xylene and ethanol. Urine samples were collected during exposure and at unspecified time intervals until the morning following exposure and analyzed for total conjugates of methylbenzoic acid. At certain time points 2,4-xylenol was also assayed. In group C, blood samples were drawn and analyzed for ethanol and acetaldehyde.

Conclusions were that disturbance in xylene metabolism was apparent and appeared to be the results of ethanol-mediated inhibition of microsomal xylene metabolism. This was based on a 1.5- to 2-fold increase in blood xylene following ethanol exposure when compared with exposure to equivalent concentrations of m-xylene alone in addition to a 50% reduction in urinary methylhippuric acid excretion in subjects exposed to both ethanol and xylene. Clear effects on 2,4-xylenol excretion were not observed. In ethanol- and xylene-exposed individuals no effects on ethanol elimination were seen; however, increased levels of blood acetaldehyde were observed.

4.6. SUMMARY

Data on the pharmacokinetics of xylenes following oral exposure are limited. Inhalation and dermal exposures, however, have been studied.

Based on data that rabbits orally dosed with o-, m- or p-xylene excreted 85-90% of dose as metabolites in the urine (Bray et al., 1949), absorption of xylenes from the gastrointestinal tract appears complete. Pulmonary absorption by humans is ~64% efficient (Astrand et al., 1978; Riihimaki et al., 1979a,b; Sedivec and Flec, 1974, 1976; Gamberale et al., 1978; Senczuk and Orlowski, 1978). Absorption of xylene vapor through the skin is much slower than pulmonary absorption and appears to represent 1-2% of that absorbed through the lungs (Riihimaki and Pfaffli, 1978). Absorption as high as 9.6 mg/cm²/hour for pure xylene applied to the forearm was reported (Dutkiewicz and Tyras, 1968).

Distribution of xylene throughout the body appears rapid (Carlsson, 1981). Bioaccumulation may occur in the adipose tissue during high-level or extended xylene exposure, but most xylene is cleared rapidly from the body since it is metabolized. The half-life of m-xylene in adipose tissue following exposure to 100 ppm (434 mg/m^3) (6 hours/day for 6 days) was 47.5 hours (Engstrom and Riihimaki, 1979). Savolainen et al. (1979a) reported that accumulation of xylene in the perirenal fat of rats exposed by inhalation was initially high (after 5 weeks of exposure), but decreased with longer exposure durations. After cessation of exposure, xylene eliminated from subcutaneous fat with a half-life of 2-3 days.

In animals and humans, xylene isomers are predominantly (85-95% of absorbed dose) metabolized by oxidation of one of the methyl groups, yielding toluic acid, which is then conjugated for urinary excretion. Evidence from animal and human studies indicates that both m- and p-toluic acid metabolites are conjugated with glycine forming m- or p-methylhippuric acid, respectively. In animals, o-toluic acid conjugates equally well with glucuronide, resulting in both o-methylhippuric and o-toluyl glucuronide in the urine. In humans, o-toluic acid appears to be conjugated primarily with glycine so that o-methylhippuric acid predominates. Aromatic hydroxylation of all xylene isomers represents a minor (1-2%) metabolic pathway in animals and humans.

Elimination of xylenes is primarily through urinary excretion of metabolites, which may represent ~95% of the absorbed dose. Exhalation of unchanged xylene from the lungs may represent 5% of the absorbed dose. In humans exposed to m-xylene by inhalation at 600 mg/m^3 (138 ppm) for 8 hours, the maximal urinary excretion rate was 350 mg/hour. Excretion rate was related to the absorbed dose and did not appear to be saturated at this level of exposure (Senczuk and Orlowski, 1978). Excretion was nearly complete within 30 hours of exposure and the chance of accumulation was slight. Urinary elimination was described as a three-phase process, with respective half-times at 1-2, 10 and 20 hours. The slowest phase only became evident after prolonged xylene exposure, possibly indicating clearance of accumulated xylene from the adipose tissue (Riihimaki et al., 1979a,b). Pulmonary elimination was a two-phase process, with half-times of 0.5-1 and 20 hours, respectively.

A number of investigators have shown that the individual isomers of xylene are inducers of cytochrome P-450 system (Toftgard and Nilsen, 1982; Toftgard, 1983; Elovaara, 1982; Pyykkö, 1980; Ungvary et al., 1980; Patel, 1978). All isomers induced hepatic and lung microsomes while in the kidney microsomal P-450 activity was increased by exposure to o- or m-xylene. Experiments were performed that indicated xylene induces hepatic isozymes very similar, if not identical, to that induced by phenobarbital (Toftgard, 1983; Toftgard and Nilsen, 1982; Toftgard et al., 1983a,b). Exposure to p-xylene by either oral, inhalation or intraperitoneal injection decreased pulmonary microsomal p-xylene hydroxylase activity but not hepatic (Patel, 1978).

5. EFFECTS

5.1. CARCINOGENICITY

5.1.1. Animal Studies. A 2-year bioassay of mixed xylenes (60.2% m-xylene, 13.6% p-xylene, 17.0% ethylbenzene and 9.1% o-xylene) was available as a board draft (NTP, 1986). Groups of 50 male and 50 female F344/N rats and 50 male and 50 female B6C3F1 mice were treated by gavage with mixed xylenes in corn oil. The chemical was administered 5 days/week for 103 weeks at dosages of 0, 250 or 500 mg/kg/day for rats and 0, 500 or 1000 mg/kg/day for mice. These dose levels were chosen based on evidence of reduced body weight gain and clinical signs at higher doses in subchronic experiments. In the chronic study, surviving animals were killed after 104-105 weeks. Gross necropsy and comprehensive histological examinations were performed on all rats and mice that died or were killed when moribund during the study or that were killed at the end of the study, unless precluded by cannibalism or advanced autolysis. There was a dose-related increased mortality in male rats (36/50 control, 26/50 low-dose and 20/50 high-dose male rats survived until the end of the study); however, many of the early deaths were caused by gavage errors. No significant differences in mortality were observed for female rats or male and female mice. Interstitial cell tumors of the testis were observed in 43/50 control, 38/50 low-dose and 41/49 high-dose male rats. Although the tumor incidences in the low- and high-dose groups were not significantly different compared with controls by the Fisher Exact test, significant differences for the high-dose group were obtained by life table tests ($p<0.001$) and incidental tumor tests ($p=0.027$), which adjust for survival. NTP (1986) explained that the apparent effect was due to an occurrence of interstitial cell tumors in 13/13 high-dose male that died during weeks 62-92, compared with 4/9 vehicle controls dying during the same period. No differences were found for other time intervals; therefore, the effect was probably not compound-related. No increased incidences of tumors were found among treated female rats or treated male and female mice when compared with controls by any statistical test. NTP (1986) concluded that under the conditions of the bioassay there was no evidence of carcinogenicity of mixed xylenes in rats or mice.

NTP (1986) reviewed a study by Maltoni et al. (1985) in which groups of 40 male and 40 female Sprague-Dawley rats were treated by gavage with xylenes in olive oil at 0 of 500 mg/kg/day, 4 or 5 days/week for 104 weeks. The rats were then observed until they died or until the study was terminated at 141 weeks. The incidence of total malignant tumors (not otherwise specified) was 10/50 female controls, 22/40 dosed females, 11/50 control males and 14/40 dosed males. Because the Maltoni et al. (1985) study was concerned primarily with benzene, the data for xylenes were not reported completely. NTP (1986) stated that without information on survival and specific tumor type, the study is difficult to interpret.

In a study of the carcinogenic potential of various aromatics on the skin, xylene was tested in 40 white mice (strain not specified) (Berenblum, 1941). Undiluted xylene was applied to the clipped skin between the shoulder blades (the volume of xylene applied was not reported) once weekly for 25 weeks. Four mice died during the study and only 1 of the 36 survivors developed an application-site papilloma (appearing at 20 weeks). This study also suggested that xylene, when used as a solvent for benzopyrene, did not augment carcinogenicity.

Pound and Withers (1963) administered 0.25 mℓ of undiluted xylene to the right side of the back of male "Hall strain" mice, 1-6 days before injection with urethane at the midline of the back. Croton oil was applied to the back once a week for 20 weeks. An increased tumor yield was noted on the right side of the back as compared with the untreated left side. These researchers concluded pretreatment with xylene increased tumor yield. Since no group was treated with xylene without urethane, this experiment does not determine whether xylene or urethane was acting as an initiator.

Pound (1970) treated a group of 40 Hall strain mice with 0.25 mℓ of xylene on the left side of the back followed by promotion with croton oil (applied once weekly for 30 weeks). Four of the 28 xylene-initiated mice surviving 35 weeks had tumors, while 5/24 mice treated with croton oil alone and surviving 35 weeks had tumors. It was concluded that xylene did not act as an initiator.

5.1.2. **Human Studies.** McMichael et al. (1975) reported a case-control study that revealed a statistically significant positive association between exposure to organic solvents and leukemia; however, they did not associate the leukemias with specific solvents. Subsequently, Arp et al. (1983) estimated the worker exposure to the individual solvents from the records of the company studied by McMichael et al. (1975). Of the 15 cases of leukemia in the McMichael et al. (1975) study, 6 cases of leukemia were associated with xylene exposure. Arp et al. (1983) stated that records indicated that coal-based xylene was the primary component of a crude naphtho, which is a mixture of solvents. The nature of the other solvents was not specified. Compared with matched case-controls, the relative risk was 5.5 ($p<0.02$). Exposure levels, however, were not quantified and the relative risks were calculated from a small sample size as well as a possible misclassification of exposed workers and a lack of consideration of latency factors.

Olsson and Brandt (1981) reported that 23/61 patients with non-Hodgkin's lymphoma were exposed to organic solvents (xylene, benzene and toluene) for at least 1 year. The smoking and drinking habits of the exposed and nonexposed patients were similar.

5.2. MUTAGENICITY

Mutagenicity studies on the xylenes indicate that the specific isomers are nonmutagenic (Table 5-1).

Florin et al. (1980) reported that m- and p-xylene did not induce reversions of the mutant strains, TA98, TA100, TA1535 and TA1537 of Salmonella typhimurium with or without metabolic activation systems prepared from the livers of rats induced with 3-methylcholanthrene or Aroclor 1254.

NTP (1986) also reported negative results for mixed xylenes in S. typhimurium strains TA100, TA1537, TA97 and TA98 and for o-, m- and p-isomers in TA100, TA1537, TA1538 and TA98 with and without the S-9 fraction prepared from Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. All three isomers of xylene were negative in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 when tested in the absence and presence of an activation system prepared from livers of untreated rats or Aroclor 1254-pretreated rats.

McCarroll et al. (1981) obtained negative results in the rec assay with technical xylene (composition not specified) in Escherichia coli mutant strains WP2, WP2 urvA, WP67, WP100, CM611, W3110 (pol A^+) and p3478 (pol A^-).

Xylene has been tested in various eukaryotic systems as well. Donner et al. (1980) reported that m- and o-xylene were not mutagenic in the Drosophila recessive lethal test. Technical xylene, which contained up to 18.3% ethylbenzene, was observed to be weakly mutagenic, causing 1-5% recessive lethals. Pure ethylbenzene, however, did not cause an increase in the

TABLE 5-1

Mutagenicity Testing of Xylene

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	*Salmonella typhimurium* TA98, TA100 TA1535, TA1537	m-xylene	plate	3, 32, 320 and 3200 µg/ plate	±S-9	–	Toxic to bacteria at 3200 µg/plate	Florin et al., 1980
Reverse mutation	*S. typhimurium* TA98, TA100 TA1535	p-xylene	plate	3, 32, 320 and 3200 µg/ plate	±S-9	–	Toxic to bacteria at 3200 µg/plate	Florin et al., 1980
Reverse mutation	*S. typhimurium* TA100, TA1535 TA97, TA98	mixed xylenes (see Section 5.1. for composition)	plate	0, 3, 10, 33, 100 and 200 µg/plate	±S-9	–	Slightly toxic at ≥100 µg/plate	NTP, 1986
Reverse mutation	*S. typhimurium* TA100, TA1535 TA1537, TA98	o-xylene	plate	0, 1.0, 3.3, 10.0, 33.0, 100.0 and 333 µg/plate	±S-9	–	Slightly toxic at 333 µg/plate	NTP, 1986
Reverse mutation	*S. typhimurium* TA100, TA1535 TA1537, TA98	m-xylene	plate	0, 0.3, 1, 3, 10 and 33 µg/plate	±S-9	–	NC	NTP, 1986
Reverse mutation	*S. typhimurium* TA100, TA1535 TA1537, TA98	p-xylene	plate	0, 1, 3.3, 10, 33, 100 and 200 µg/plate	±S-9	–	Slightly toxic at 200 µg/plate	NTP, 1986
Reverse mutation	*S. typhimurium* TA98, TA100 TA1535, TA1537, TA1538	o-xylene	plate	20, 50, 100, 200 and 500 µg/plate	±S-9	–	NC	Bos et al., 1981
Reverse mutation	*S. typhimurium* TA98, TA100 TA1535, TA1537, TA1538	m-xylene	plate	20, 50, 100, 200 and 500 µg/plate	±S-9	–	NC	Bos et al., 1981
Reverse mutation	*S. typhimurium* TA98, TA100 TA1535, TA1537, TA1538	p-xylene	plate	20, 50, 100, 200 and 500 µg/plate	±S-9	–	NC	Bos et al., 1981

TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Rec assay	*Escherichia coli* WP2, WP2 uvr A, CM611, WP67, WP100, W3110 p3478	technical xylene	microtiter plate and glass tubes	starting at 1314 or 1752 μg/well with 11, 2-fold dilutions	±S-9	±	NC	McCarroll et al., 1981
Recessive lethal	*Drosophila melanogaster*	m-xylene o-xylene technical xylene	NR	NR	NA	- - weakly mutagenic	NC 1-5% recessive lethals observed	Donner et al., 1980
Chromosomal aberrations	rats	xylene mixture	inhalation	300 ppm (1303 mg/m^3), 6 hours/ day, 5 days/ week for 9, 14 and 18 weeks	NA	-	Number of rats exposed and marrow cells analyzed were not reported	Donner et al., 1980
Chromosomal aberrations	human lymphocytes *in vitro*	xylene	whole blood cultures	15.2, 152, 1520 μg/mℓ untreated	none	-	NC	Gerner-Smidt and Friedrich, 1978
Chromosomal aberrations	group of 17 painters	xylene and 10 other solvents	NR	25 ppm (109 mg/m^3)	NA	-	NC	Haglund et al., 1980

NR = Not reported; NA = not applicable; NC = no comment recessive lethal frequency above spontaneous levels. Further discussion of the apparent weak mutagenicity of technical xylene was not reported.

Donner et al. (1980) also reported that the number of chromosome aberrations in hematopoietic cells of the bone marrow was not elevated in rats treated with xylene.

Xylene (composition not specified) had no effect on the frequency of occurrence of SCEs in human lymphocytes _in vitro_ (Gerner-Smidt and Friedrich, 1978). No increases in the occurrences of SCEs and chromosomal aberrations in peripheral lymphocytes were observed in a group of 17 painters exposed to xylene at ~25 ppm (109 mg/m^3) in addition to 10 other solvents (Haglund et al., 1980).

In addition to the studies summarized in Table 5-1, U.S. EPA (1979) reviewed studies by Litton Bionetics (1978a). Negative results were obtained in mutagenicity assays of xylene in _S_. _typhimurium_ (five strains tested) and _Saccharomyces_ _cerevisiae_ D4 with and without rat liver activation. A dose response was observed in the L5178Y TK mouse lymphoma assay with metabolic activation; however, the increase in mutant frequency in this system was within the range of historical negative control values, and it was concluded that xylene was not mutagenic in the mouse lymphoma assay (Litton Bionetics, 1978a). U.S. EPA (1979) reported that the main defects of the study were "low mutant frequency for positive controls, a lack of test points between 38% survival and 0.8% survival in the cells with activation, and a low negative control background frequency, especially in the cells with activation." In addition to these studies, Litton Bionetics (1978a) performed a test to detect chromosome aberrations in the bone marrow cells of rats treated with xylene. No significant increase in the number of aberrations was observed in the xylene-treated rats compared with DMSO-treated controls.

5.3. TERATOGENICITY

Mixed xylene (60.2, 13.6, 9.1 and 17.0% of m-, p- and o-xylene and ethylbenzene, respectively) was administered by gavage in cottonseed oil to pregnant CD-1 mice (15-38/dose level) on days 6-15 of gestation (Marks et al., 1982) (Table 5-2). Xylene solutions (2, 4, 8, 10, 12 and 16% in cottonseed oil) were given at 10 mℓ/kg 3 times/day to provide total daily doses of 0.52, 1.03, 2.06, 2.58, 3.10 and 4.13 g/kg/day. A group of 66 dams received only cottonseed oil and served as a control group. Xylene at 4.13 g/kg/day was lethal to 15/15 dams, while 12/38 mice treated at 3.10 g/kg/day died. Signs of maternal toxicity were reported in mice treated at 3.10 g/kg/day (decreased maternal weight gain), 2.58 and 2.06 g/kg/day (increased relative liver weights). Fetal weights were also significantly ($p<0.05$) decreased in litters of mice treated at doses of ≥ 2.06 g/kg/day of mixed xylene. The number of implantation sites was not affected by xylene, but there was a significant [3.10 g/kg/day ($p<0.05$)] dose-related increase in resorptions. Wavy ribs were prevalent in the fetuses of dams treated at 2.58 and 3.10 g/kg/day and incidences of cleft palates were increased at xylene levels of ≥ 2.06 g/kg/day. There was a significant ($p<0.001$) dose-related trend for increased percent of malformed fetuses. Doses of 1.03 and 0.52 g/kg/day had no apparent effects on fetal or maternal toxicity.

Nawrot and Staples (1981), as reported in an abstract, gavaged mice with m-, o- or p-xylene 3 times/day on days 6-15 of gestation at doses of ~780, 1960, 2610 mg/kg/day. At the two highest doses of o- and p-xylene, maternal toxicity, increased resorptions and cleft palates were observed. No cleft palates or signs of maternal toxicity were observed with m-xylene. All isomers given at doses of 2610 mg/kg/day during days 12-15 of gestation increased prenatal deaths and only the m- and p-isomers resulted in cleft

TABLE 5-2

Oral Teratogenicity Testing of Xylene in CD-1 Mice[a,b]

Compound	No. of Dams at Start	Daily Dose	Maternal Response	Fetal Response
Mixed xylene (60.2, 13.6, 9.1 and 17.0% m-, p- and o-xylene and ethylbenzene)	15	4.13 g/kg/day	mortality 15/15	NA
	38	3.10 g/kg/day	mortality 12/38; decreased weight gain; reduced uterine weight; 62% resorptions	7 cleft palates: significantly increased ($p<0.01$) percent of malformations; decrease fetal weight ($p<0.05$)
	26	2.58 g/kg/day	increased ($p<0.05$) liver weight; 20% resorptions; no deaths	11 cleft palates: significantly increased ($p<0.01$) percent of malformations; decrease fetal weight ($p<0.05$)
	26	2.06 g/kg/day	increased ($p<0.05$) liver weight; 19% resorptions; no deaths	6 cleft palates: 1 exencephaly; significantly increased ($p<0.01$) percent of malformations; decrease fetal weight ($p<0.05$)
	23	1.03 g/kg/day	no significant signs of maternal toxicity; 16% resorptions	1 cleft palate; 2 fused rib arches; no significant increase in percent malformations; fetal weight comparable to controls
	24	0.52 g/kg/day	no significant toxic effects; 16% resorptions	2 fused sternebrae; no significant increase in malformations; fetal weight comparable to controls

TABLE 5-2 (cont.)

Compound	No. of Dams at Start	Daily Dose	Maternal Response	Fetal Response
Vehicle	66	10 mℓ/kg/day	11% resorptions; 15.6 g average uterine weight; 2.2 g average liver weight; no mortality	average 0.3% malformed fetuses 0.982 g average fetal weight

[a] Source: Marks et al., 1982

[b] Vehicle was cottonseed oil. Treatment was on days 6-15 of gestation; there were 18 days of observation.

palates. In additional trials with m-xylene only during days 12-15 of gestation, a dose of 2610 mg/kg/day did not result in cleft palates but exposure on days 6-15 was associated with a statistically significant (although low) increase in cleft palates. These studies support the finding of Ungvary et al. (1980) in that prenatal toxic effects including mortality were seen at high doses of individual isomers. However, Ungvary et al. (1980) did not report cleft palates but this difference may be due to differences in dosing route and species.

Inhalation teratology studies of xylenes are summarized in Table 5-3. Shigeta et al. (1983), in an abstract, reported data from a fetotoxicity study in which ICR strain mice were exposed to xylene (formulation or isomer not specified) by inhalation. Exposure was at 500, 1000, 2000 and 4000 ppm (2171, 4342, 8684 and 13,369 mg/m^3) for 6 hours/day on days 6-12 of gestation. On day 17 of gestation, two-thirds of the dams in each group (number not specified) were sacrificed and their uteri were examined for implantation and resorption sites, while fetuses were weighed and examined for external and skeletal malformations. The remaining dams were allowed to deliver and the neonates were observed for abnormal development. The numbers of implantation sites, resorbed fetuses, dead fetuses and external malformations in fetuses were not different between any of the exposure groups and an air-exposed control group. Fetal weights were decreased in mice exposed to 2000 and 4000 ppm xylene and a dose-related trend of delayed ossification and development of a 14th rib were reported. Among the neonates exposed to 4000 ppm, decreased weight gain and delayed body hair and tooth development were attributed to xylene exposure. Additional details concerning this study were not reported.

TABLE 5-3

Inhalation Teratogenicity Testing of Xylene

Compound	Species/ Strain	No. of Dams at Start	Exposure Concentration	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Xylene	mice/ICR	NR	4000, 2000, 1000, 500, 0 ppm, (17,369, 8684, 4342, 2171, 0 mg/m³), 6 hours/day	days 6-12 of gestation	17	NR	Decreased fetal weight at 2000 and 4000 ppm; decreased neonatal weight gain and hair and teeth growth at 4000 ppm; dose-related delay of sternebrae ossification and 14th rib development	Shigeta et al., 1983
Mixed xylene (50, 20, 10 and 20% m-, p-, o-xylene and ethylbenzene)	rat/CFY	20	1000 mg/m³ (230 ppm), 24 hours/day	days 9-14 of gestation	21	no toxic effects were observed	Significantly increased fused sternebrae and extra ribs; trend of retarded skeletal development evident	Hudak and Ungvary, 1978
o-Xylene	rat/CFY	20, each dose group	150, 1500, 3000 mg/m³, 24 hours/day (35, 350, 700 ppm)	days 7-14 of gestation	21	significantly increased relative liver weight ($p<0.05$) at all doses	Decreased fetal weight in two higher dose groups ($p<0.001$); 13% fetal loss at highest dose level; skeletal retardation evident at highest dose level	Ungvary et al., 1980a
m-Xylene	rat/CFY	20, 20, 30, respectively	150, 1500, 3000 mg/m³, 24 hours/day	days 7-14 of gestation	21	significantly reduced maternal weight gain and implantations/dam at highest dose level; mortality 4/30 at highest dose level	significantly reduced fetal weight ($p<0.01$) at highest dose level	Ungvary et al., 1980a
p-Xylene	rat/CFY	20, each dose group	150, 1500, 3000 mg/m³, 24 hours/day	days 7-14 of gestation	21	significantly reduced mean litter size and placental weight at highest dose ($p<0.001$)	Significantly reduced fetal weight at highest dose level ($p<0.001$); 69% fetal loss (resorption) at highest level; skeletal retardation evident at all dose levels	Ungvary et al., 1980a
p-Xylene	rat/CFY	20, each treatment schedule	3000 mg/m³, 24 hours/day	day 10 or 9-10 of gestation	9-10	significantly decreased levels of peripheral estradiol and progesterone ($p<0.05$) after 48 hours of exposure	Decreased fetal weight after 48 hours of exposure	Ungvary et al., 1981

TABLE 5-3 (cont.)

Compound	Species/ Strain	No. of Dams at Start	Exposure Concentration	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Xylene mixture (o-xylene 10%, m-xylene 52.1%, p-xylene 0.31%, ethylbenzene 36.1%, toluene 0.12%)	rats/CRL: COBS CD(SD)BR	24-26	0, 100 or 400 ppm (0, 434 or 1737 mg/m^3) 6 hours/day	days 6-15 of gestation	20	food consumption and weight gain were normal; no signs of maternal toxicity	No significant increases in fetal malformations; no effect on fetal weight or sex ratios; at the high dose, there was a statistically significant increase in retarded ossification of the skull and vertebrae and sometimes other bones not treatment-related	Litton Bionetics, 1978b
Xylene mixed isomers (composition not specified)	rats/NR	NR	230, 1900 or 3360 mg/m^3 24 hours/day	days 7-14 of gestation	NR	no effects	Delayed bone development at all concentrations, dose-related increased incidence of extra ribs and post-implantation loss	Balogh et al., 1982
Xylene mixture (o-xylene 20.42%, m-xylene 44.2%, p-xylene 20.3%, ethylbenzene 12.8%, toluene 2.4%)	rats/CD	20 (M&F)	0 or 500 ppm (0 or 2171 mg/m^3) 6 hours/day	130 days before mating, mated females exposed for days 1-20 of gestation	day 21 of gestation	no treatment related effects on body weight, physical characteristics, food consumption. No effects observed in post-mortem data except an increased kidney weight	Statistically significant, weight decrease in female fetuses; variation in ossification	Bio/Dynamics, 1982
Xylene mixed isomers (composition not specified)	rat/Wistar	15-36	0, 10, 50 and 500 mg/m^3 6 hours/day, 5 days/week	1-21 of gestation	day 21 of gestation and at 1 and 3 months after birth	NR	At 500 mg/m^3, significant increased incidences of hydrocephalus microphthalmia and intracerebral hematoma, dilatations of aorta and auricles of heart; at 50 and 500 mg/m^3, statistically significant increased incidence of postimplantation losses ($p<0.05$) and hemorrhages ($p<0.01$); decreased mean fetal weight ($p<0.05$); abnormal ossification of sternum; impaired formation of skull; unspecified skeletal defects observed at 10 mg/m^3	Mirkova et al., 1983

NR - Not reported

The embryotoxicity of mixed xylene (50, 20, 10 and 20% m-, p- and o-xylene and ethylbenzene, respectively) was tested in CFY rats (240-280 g) exposed continuously by inhalation from day 9-14 of gestation (Hudak and Ungvary, 1978). Pregnant rats were exposed to 1000 mg/m³ (n=20) and compared with air-exposed (n=26) and untreated (n=28) controls. Maternal weight gain, mean litter size, mean placental weight and mean fetal weights were not different between exposed and control groups. Fetal loss (resorbed and dead fetuses) was 5.60% (16/286) among xylene-exposed dams, while that in air-exposed and untreated controls was 4.13% (15/348) and 3.37% (11/326), respectively. This difference, however, was not statistically significant. The incidences of fused sternebrae and extra ribs were 8/286 and 9/286, respectively, in xylene-exposed pups, 1/315 and 2/315, respectively, in untreated controls and 2/348 and 0/348, respectively, in air-exposed controls. The differences were significant ($p<0.005$). An increasing trend of retarded skeletal development was also evident among xylene-exposed rats when compared with controls; however, this was not statistically significant. Visceral malformations were not increased among the xylene-exposed fetuses.

The embryotoxic potencies of the three xylene isomers were determined and compared in studies conducted by Ungvary et al. (1980a). Pregnant CFY strain rats were exposed by inhalation to o-, m- or p-xylene vapor (analytical purity) at 150, 1500 or 3000 mg/m³ (35, 350 or 700 ppm) continuously on days 7-14 of gestation. The number of rats exposed in each isomer concentration group was 20, except for m-xylene at 3000 mg/m³, which contained 30 rats. A group of 15, 25 or 20 pregnant rats exposed to clean air served as controls for the o-, m- or p-xylene-exposed groups, respectively. Exposures were conducted in inhalation chambers (0.4 m³ volume) at a flow rate of 5 m^3/hour at regulated temperature (24-25°C) and humidity (50-55%). Rats were sacrificed on day 21 of gestation and parameters indicative of maternal and fetal toxicity were measured. Signs of maternal toxicity included decreased food consumption after exposure to 1500 mg/m^3 (o-xylene only) and 3000 mg/m^3 (all three isomers), mortality (m-xylene at 3000 mg/m^3), decreased weight gain (m-xylene, all levels) and increased relative liver weight (o-xylene, all levels). Decreased fetal weights were evident in groups exposed to 1500 mg/m^3 (o-xylene only) and 3000 mg/m^3 (all isomers). Postimplantational fetal loss, which was due to resorption, was significantly ($p<0.01$) increased in rats exposed to p-xylene at 3000 mg/m^3. Preimplantational loss of embryos, indicated by an increase in nonpregnant dams or a decrease in the number of implants per pregnant rat, was increased in dams exposed to m-xylene at 3000 mg/m^3 and p-xylene at all concentrations.

Macroscopic examinations were conducted on fetuses to identify external, visceral and skeletal malformations (Ungvary et al., 1980a). The most prominant effects were "signs of skeletal retardation" (assumed to be delayed ossification) and extra ribs. No increase in external, internal or skeletal malformations was reported. Histological examinations of "representative organs," enzymatic determinations of the liver, kidney and thymus, and electronmicroscopic studies of the liver were conducted on five, three and three representative fetuses from each dose group, respectively, for each isomer. No xylene-related histological changes were evident in any group. Renal alkaline phosphatase (proximal convoluted tubules), succinic dehydrogenase, acid phosphatase and glucose 6-phosphatase (nephrons) levels appeared lower in fetuses from dams exposed to o- and p-xylene at 3000 mg/m^3 compared with controls. All three isomers at 3000 mg/m^3 decreased fetal hepatic and thymic succinic dehydrogenase and glucose-6-phosphatase.

The decreased levels of renal, hepatic and thymic enzymes were regarded as indicative of retardation of maturation of the enzyme synthesis system. Ungvary et al. (1980a) also found that the content of o-xylene in maternal and fetal blood after exposure day 18 was proportional to the exposure level of the pregnant dams, suggesting that xylene crosses the placenta. Supportive evidence was reported by Tatrai et al. (1979), Ungvary et al. (1979a) and Hudak et al. (1980).

In an attempt to determine whether p-xylene-induced embryotoxicity could be attributed to its effects on ovarian and uterine circulation and hormone production, Ungvary et al. (1981) treated pregnant CFY rats (220-240 g) on day 10 or days 9 and 10 of gestation. p-Xylene was administered by inhalation at 3000 mg/m^3 (700 ppm) to 20 animals for 24 hours/day. Two hours after exposure was terminated, rats were anesthetized and the uteri and ovaries were cannulated by the utero-ovarian veins. Blood flow and levels of 17β-estradiol and progesterone were determined. The uteri were then removed and weighed and the embryos counted and weighed. Ovarian blood flow appeared lower after 48 hours of exposure, but the decrease was not statistically significant; uterine blood flow was not changed. Fetal weights decreased with exposure duration. After 48 hours, the decrease was significant ($p<0.01$), but placentas appeared normal (gross and histologically). Ovarian progesterone and estradiol secretion rate was not significantly affected by p-xylene exposure for either duration. Levels of progesterone and estradiol detected in the uterine vein were significantly ($p<0.05$) decreased in rats exposed for 48 hours. Ungvary et al. (1981) concluded that the delayed fetal development was not due to altered uterine circulation, and that hormone production (by the ovary) was not affected, but peripheral circulatory hormone levels were decreased. The p-xylene may, therefore, cause more rapid hormone metabolism by the hepatic mixed function oxidase system, leading to decreased peripheral hormone titers and the embryotoxic effects.

Balogh et al. (1982) exposed pregnant rats by inhalation to xylene at 230, 1900 or 3360 mg/m^3 (52, 436 or 772 ppm) for 24 hours/day on days 7-14 of gestation. No maternal toxic effects were reported. Delayed bone development of fetuses was observed at all three concentration levels. The incidence of extra ribs was increased and fetal renal enzyme activities including alkaline and acid phosphatase and succinic dehydrogenase were decreased. The incidence of resorptions (postimplantational fetal loss) was increased in exposed litters.

Mirkova et al. (1983) exposed groups of 15-36 pregnant Wistar rats by inhalation to 0, 10, 50 and 500 mg/m^3 (0, 1, 11.5 and 115 ppm) of a xylene mixture, 6 hours/day, 5 days/week on days 1-21 of gestation. At 50 and 500 mg/m^3, there was a statistically significant increased incidence of postimplantation loss ($p<0.05$) and hemorrhage, particularly of the cervical region ($p<0.01$), and a significant decrease ($p<0.05$) in mean fetal weight. After birth, weights were still lower in these rats. At 500 mg/m^3, there were anomalies of the internal organs (hydrocephalus, microphthalmia, intracerebral hematomas, dilatations of the aorta and auricles of the heart). At 50 and 500 mg/m^3, abnormal ossification of the sternum and impaired formation of the skull was observed. Increased incidences of skeletal defects were also observed at 10 mg/m^3. However, since the actual incidences of these skeletal and visceral findings were not reported, a teratogenic response cannot be adequately evaluated. The relatively low conception rates and the high incidence of fetal hemorrhage even in controls suggest that the general health of the animals may have been compromised (Hood and

Otley, 1986). Data for pups sacrificed at 7 and 21 days postpartum indicated that pups from mothers exposed to 50 and 500 mg/m³ weighed significantly less than controls and had metabolic disturbances in such organs as the liver, brain, heart and lungs. Prenatal exposure to 500 mg/m³ was associated with postnatal deficiencies in hepatic excretory function and behavioral activity.

In a Litton Bionetics (1978b) study, rats (average weight = 263 g) were exposed by inhalation to a xylene mixture at levels of 0, 100 or 400 ppm (0, 434 or 1737 mg/m³), 6 hours/day on days 6-15 of gestation. Food consumption and weight gain were normal in the dams and no signs of maternal toxicity were observed. Fetal malformations were not significantly increased, and fetal weights or sex ratio were unaffected. An increase in resorptions and an increase in litters with at least one resorbed fetus was observed in the high-dose group, but this was not statistically significant compared with concurrent or historic controls. A statistically significant increase in incidences of fetuses with delayed ossification of the skull, vertebrae and sometimes other bones was observed in the high-dose group. The affected fetuses had reduced weights as well. As these effects were seen in only 3/25 litters examined, they were not considered treatment-related by the authors.

In a reproduction study by Bio/Dynamics (1982) (Section 5.4.), groups of male and female CD rats were exposed by inhalation to 0 or 500 ppm (0 or 2171 mg/m³) of a xylene mixture, 6 hours/day for 130 days before mating and during the mating period; females continued to be exposed during days 1-20 of gestation. On day 21 of gestation, the control and exposed dams (20/group) were sacrificed. No signs of maternal toxicity were observed.

There were no significant differences in the number of corpora lutea, implantation sites, resorption sites or percentage of resorption/implants, number of live fetuses or percentage of live fetuses/implants, fetal sex distribution, incidence of external fetal malformations, fetal soft tissue malformations or skeletal variations. There was a statistically significantly decreased mean fetal body weight of exposed female fetuses compared with controls. Exposed fetuses had a slightly higher incidence of unossified sternebrae and incompletely ossified cervical vertebral transverse processes.

In a study of the embryotoxic effects of laboratory reagents, Overman (1981) reported that xylene caused minimal effects in the embryos and more extensive effects on maternal skin. Xylene (isomer or mixture not specified) was applied to the shaved backs of hamsters for exposure periods of 2 hours between days 7 and 11 of gestation. It is not clear whether xylene was applied to the skin on one or all days throughout the period, and the dose and number of hamsters treated were not specified. Effects reported generally for all reagents tested included decreased fetal size and weight, increased prenatal death and unspecified cases of fetal hemorrhage and gastroschisis.

Mirkova et al. (1979) dermally treated pregnant rats with xylene (not otherwise specified) at 0, 100, 200 or 2000 mg/kg/day for the first 20 days of gestation. Cholinesterase and cytochrome oxidase activity in the maternal brain declined at all levels, but in the high-dose group, glucose-6-phosphate dehydrogenase activity was increased. Maternal DNA and soluble protein were lower in the 200 and 2000 mg/kg/day groups, but the reason for such a discrepancy was unclear. In the high-dose groups, maternal open field activity and "emotionality" (measured by the number of defecations) were altered. The cholinesterase and cytochrome oxidase activities of fetal brains were inhibited at 200 and 2000 mg/kg/day. Increased maleate, isocitrate and glucose-6-phosphate dehydrogenase activities were also noted.

Rumsey et al. (1969) treated a group of pregnant rats with a 1:1 mixture of xylenes and alkylphenoxy polyethoxyethanol, which was used as a solvent for an insecticide. A mixture of xylenes was used as a control. On gestation days 6, 9 or 12, the pregnant females were immersed up to their heads in the solvent mixture. There were no effects on female fertility and no adverse effects in fetuses.

5.4. OTHER REPRODUCTIVE EFFECTS

In an extensive reproduction study by Bio/Dynamics (1982), groups of 10 male and 20 female CD rats were exposed to a xylene mixture (20.42% o-xylene, 44.2% m-xylene, 20.3% p-xylene, 12.8% ethylbenzene and 2.4% toluene) by inhalation at concentrations of 60, 250 or 500 ppm (0, 261, 1086 or 2171 mg/m^3), 6 hours/day. Males were exposed for 130 days before mating and during the mating period. After mating, five males from each group were sacrificed and necropsied and the remaining five/group were allowed a 3-week recovery period before sacrifice. Females were exposed for 130 days before mating, during the mating period, on days 1-20 of gestation and on days 5-20 of lactation. During the lactation period, a crossfostering experiment was performed. The females were killed and necropsied after the pups were weaned. Pups were killed and necropsied at 21 or 49 days after birth. Additional groups of males and females were exposed to 500 ppm according to the above schedule, except that all females (control and treated females) were sacrificed on day 21 of gestation for teratogenicity evaluations (see Section 5.3.). In a special mating experiment, 10 additional males that were exposed to 500 ppm according to the above schedule were mated to nonexposed females and 20 additional females that were exposed to 500 ppm according to the schedule were mated to nonexposed males. There were no treatment-related effects on mortality, body weight gain, food consumption or gross necropsy data of the parental rats. The weights and histological appearance of male reproductive organs were not affected. No treatment-related effects were observedon mating, pregnancy or fertility indices, gestation length or parturition data, litter size or pup survival. Mean pup weights were significantly decreased on day 21 of lactation in the 500 ppm group compared with controls. In the 250 and 500 ppm female pups, mean ovary weights were lower than controls at day 21 but not at day 49 after birth. Gross and histological examinations of pups at 21 days after birth were unremarkable.

Ungvary and Donath (1984) exposed pregnant CFY rats to 1500 mg/m^3 p-xylene for 8 hours/day between days 8 and 10 of gestation. Exposure to p-xylene caused hyperenervation and degeneration of the reproductive organs. p-Xylene injected into the anterior chamber of the eye damaged the sympathetic nerve-plexus of the iris and caused a dose-dependent hyperenervation. The authors suggested "damage to these peripheral noradrenergic fibers may result in disturbed control of ovarian and uterine blood flow and steroid production and may thus be instrumental in the embryotoxic action of organic solvents."

Washington et al. (1983) exposed male Sprague-Dawley rats to intraperitoneal injections of 0.5 or 1.5 mℓ o-xylene for 2 consecutive days. The test animals were maintained at either 20-24°C or 24-30°C room temperature for 5 weeks following treatment. At the 0.5 mℓ dose level no adverse effects were observed on sperm morphology for the animals maintained at 20-24°C. Among the animals housed at 24-30°C room temperature, there was an increased percentage of abnormal sperm when compared with controls (4.17±1.41% treated vs. 2.94±1.36% controls). No data were reported for the 1.5 mℓ dose group.

Michon (1965) reported the menstrual history of 500, 20- to 40-year-old Polish women exposed to unspecified amounts of benzene, toluene and xylene during shoe manufacturing. The duration and intensity of the menstrual flow increased, but no change in rhythm was observed when exposed women were compared with a control population.

Most of these studies on developmental toxicity have used commercial or mixed xylene isomers that contained 17-35% ethylbenzene and possibly other impurities. Ethylbenzene may have some embryotoxic and developmental effects on rats. An abstract of a Hungarian study (Tatrai et al., 1982) indicated that inhalation exposure of pregnant dams to 2400 mg/m³, 24 hours/day from day 7 to day 15 of pregnancy, caused retarded skeletal development and weight gain and an increased incidence of extra ribs in rat embryos. In conclusion, the available studies do not present convincing evidence of developmental toxicity but suggest that there is some concern and that additional research is needed.

5.5. SUBCHRONIC AND CHRONIC TOXICITY

In the 2-year carcinogenicity bioassay (see Section 5.1.), groups of 50 male and 50 female rats were treated by gavage with mixed xylenes in corn oil at 0, 250 or 500 mg/kg/day, 5 days/week for 103 weeks (NTP, 1986). Groups of 50 male and 50 female mice were similarly treated at 0, 500 or 1000 mg/kg/day. High-dose male rats had a 5-8% decreased average body weight compared with controls after week 59, which was considered to be an indication of slight toxicity. There was a dose-related increased mortality in the male rats; the difference between the high-dose and the control group was statistically significant. Many of the deaths of dosed rats were caused by gavage error; however, the possibility that the dosed rats resisted dosing by gavage because of a behaviorial effect was not ruled out. Observations on behavior during dosing were not recorded. No differences in body weights or survival were observed for mice. High-dose male and female mice were consistently hyperactive for 5-30 minutes after dosing from week 4-103. No compound-related increased incidence of histopathological lesions were observed in any groups of dosed rats or mice.

In subchronic experiments to determine the MTDs to be used in the 2-year bioassay, NTP (1986) treated groups of 10 male and 10 female F344/N rats by gavage with mixed xylenes in corn oil at 0, 62.5, 125, 250, 500 or 1000 mg/kg/day, 5 days/week for 13 weeks. Groups of 10 male and 10 female B6C3F1 mice were similarly treated at dosages of 0, 125, 250, 500, 1000 or 2000 mg/kg/day. At the end of the study, the animals were killed and gross necropsy and comprehensive histological examinations were performed. None of the rats died. The only effect observed in rats was a 15 and 8% lower body weight change than controls in the 1000 mg/kg/day males and females, respectively. In mice, two females treated at 2000 mg/kg/day died, possibly from gavage error. Male and female mice treated at 2000 mg/kg/day had weakness, lethargy, short and shallow breathing, unsteadiness, tremors and paresis at 5-10 minutes after dosing. These signs lasted 15-60 minutes. High-dose males had a 7% and high-dose females had a 17% lower mean body weight gain than did controls. There were no treatment-related gross or histopathological lesions in any group of rats or mice.

o-Xylene was administered to male Long-Evans rats (12-19 months old) in the diet at 200 ppm of feed for up to 6 months (Bowers et al., 1982).

Twenty rats weighing 0.8-0.9 kg were used in each group (exposed and control) and five animals of each group were killed after 1, 2, 3 and 6 months of exposure. Livers of sacrificed animals were fixed for electron microscopy by perfusion. Upon gross examination, the livers of all treated rats exposed for any interval tested appeared normal. Ultrastructurally, hepatocytes from rats exposed for 1, 2, 3 or 6 months had two types of vesicles not present in hepatocytes of control animals. These structures were apparent after 1 month of exposure, but did not increase in number after longer exposures. One vesicle was double membrane-bound and appeared to originate from the smooth endoplasmic reticulum. The second type of vesicle was peripherally located and appeared to fuse to the plasmalemma as in exocytosis. The first vesicle may have been of an autophagous type derived from the smooth endoplasmic reticulum and involved in elimination of the xylene. The second type was thought to be involved with increasing hepatocyte surface area or elimination of metabolites.

In the only available oral study of m-xylene, Borriston Laboratories, Inc. (1983) gave groups of 10 F-344 male rats daily doses of 0.5 or 2.0 g/kg m-xylene by gavage 5 days/week for 4 weeks. No significant effects in nephropathology were reported for either treatment group. Other parameters of toxicity were not evaluated.

Chronic exposure to o-xylene by inhalation at 4750 mg/m^3 (1090 ppm) for 8 hours/day, 7 days/week for a 1-year period caused several toxic responses in male CFY rats (Tatrai et al., 1980, 1981). Water and food consumption of exposed rats was increased throughout the study. Hepatic enzyme induction and hepatotoxicity were evident in the treated rats. Hepatic cytochrome P-450 and b-5 concentrations, NADPH-cytochrome c reductase activity, aniline hydroxylase activity and aminopyrin-N-demethylase activity were increased, while bromsulfophthalein retention time in the liver was decreased. Decreased body weight gain and hepatomegaly were reported. The livers of exposed rats appeared histologically normal. Upon ultrastructural examination, centrilobular hepatocytes appeared to have moderate proliferation of smooth endoplasmic reticulum and depletion of glycogen, with occasional mitochondrial damage and increased number of autophagous bodies and peroxisomes. Proliferation of the endoplasmic reticulum is consistent with increased enzymes of the mixed function oxidase system. o-Xylene was regarded as an inducer of hepatic enzyme metabolism and liver enlargement was attributed to functional hypertrophy during the chronic exposure (Tatrai et al., 1980, 1981).

Jenkins et al. (1970) tested the effects of subchronic inhalation of o-xylene in rats (12-14/group), guinea pigs (15/group), dogs (2/group) and monkeys (2 or 3/group) exposed continuously for 90 days at 337 mg/m^3 (78 ppm) or at 3358 mg/m^3 (780 ppm), 8 hours/day, 5 days/week for 6 weeks. Terminal body weights of all species exposed repeatedly or continuously were not different when compared with their respective controls. Hematological parameters (leukocyte count, hematocrit and hemoglobin) of rats, guinea pigs and dogs exposed to o-xylene were not different from normal values compiled from preexposure data. After necropsy, histopathological examinations of lung, liver, kidney, heart, spleen, brain and spinal cord (nervous tissue examined in dogs and monkeys only) were reported as essentially negative. On the 3rd day of exposure at 3358 mg o-xylene/m^3 (770 ppm) two rats died while another rat and one monkey died on the 7th day. One rat exposed continuously to o-xylene died on day 56. One of the dogs exposed to o-xylene at 3358 mg/m^3 exhibited neuromuscular tremors throughout the study.

Male CFY strain rats (n=30) were exposed to o-xylene by inhalation at 3500 ppm (15,190 mg/m^3), 8 hours/day (presumably 7 days/week) for 6 weeks (Tatrai and Ungvary, 1980). [Although the exposure level was reported as 3500 ppm, U.S. EPA (1984) felt that this may be in error and that 3500 mg/m^3 seems more appropriate.] A group of 30 rats inhaling pure air in a similar environment served as controls. Exposed rats consumed more food and water but had decreased body weight gains. Hepatomegaly was evident in exposed rats at necropsy. Hepatocytes, observed histologically, had enlarged nuclei and had larger cells in exposed animals compared with controls. Ultrastructurally, hepatocytes had increased rough and smooth endoplasmic reticulum and decreased glycogen content. Histochemically, centrilobular succinate dehydrogenase and glucose-6-phosphatase was decreased. Hepatic changes were regarded as adaptational. Ungvary et al. (1980b) exposed six male CFY rats to 4500 mg/m^3 (1035 ppm) of o-xylene by inhalation for 8 hours/day for 6 weeks. Cytochrome P-450 and cytochrome b-5 content was significantly increased as compared with controls ($p<0.05$), and aniline hydroxylase and aminopyrine N-demethylase activity was also significantly increased ($p<0.05$).

Slight degeneration of the liver and pulmonary inflammation were reported in three guinea pigs exposed to m-xylene (redistilled from commercial m-xylene) by inhalation (Smyth and Smyth, 1928). Exposure was initially set at 450 ppm (1950 mg/m^3), but the concentration was decreased to 300 ppm (1300 mg/m^3) because of a death among the test animals on the 1st day. Exposure was 4 hours/day, 6 days/week for 64 exposures. When similar studies were repeated, slight chronic catarrhal inflammation of the lungs and moderate renal tubular degeneration were noted in guinea pigs exposed to o-xylene at 300 ppm (1300 mg/m^3, 4 hours/day, 6 days/week) for 58 exposures. Smyth and Smyth (1928) also reported that 4/4 rats exposed at 980 ppm (4250 mg/m^3) for 7 days showed "marked effects," while rats (n=8) exposed at 620 ppm (2690 mg/m^3) for 7 days showed no ill effects. Further details were not reported.

Savolainen et al. (1979a) and Savolainen and Pfaffli (1980) studied the effects of m-xylene and a mixture of the xylene isomers in groups of 15 male Wistar rats. Brain enzyme and glutathione levels were studied to determine the mechanism of xylene neurotoxicity. m-Xylene administered at 212, 1710 and 3220 mg/m^3 for 6 hours/day, 5 days/week for 2 weeks caused decreased brain glutathione and increased NADPH-diaphorase levels, while treatment at the higher two levels also caused decreased brain superoxide dismutase and azoreductase activity (Savolainen and Pfaffli, 1980). Brain superoxide dismutase levels were decreased after 5 weeks but subsequently increased by 18 weeks of treatment with xylene isomers at 1300 mg/m^3, 6 hours/day, 5 days/week (Savolainen et al., 1979a). These authors also reported a decrease in preening activity among the treated rats during weeks 9-12 of treatment. Brain levels of protein, RNA, acid proteinase and NADPH-diaphorase did not appear to be affected by xylene treatment. Brain cytosolic glutathione peroxidase activity was decreased ($p<0.05$) compared with that in untreated control rats after 14 weeks of treatment, but returned to near control levels by 18 weeks (Savolainen et al., 1979a).

Cameron et al. (1938) exposed 10 mice and 10 rats to p-xylene vapor at 5300 mg/m^3 (1226 ppm) for 14 daily 8-hour exposures. Two groups of 10 rats each were exposed to m- or o-xylene at 4300 or 7300 mg/m^3 (1005 or 1531 ppm), respectively, for the same exposure period. All xylene isomers at these exposure levels had no apparent effects in mice or rats. It appeared, however, that toxic effects were determined by gross or behavioral signs and microscopic examination of the treated animals was not performed.

The effects of repeated daily exposure to mixed xylenes (65.0, 7.6, 7.8% m-, o- and p-xylene and 19.3% ethylbenzene) were determined in rats (n=25/group) and dogs (n=4/group) treated by inhalation at three exposure levels, 6 hours/day, 5 days/week for 13 weeks (Carpenter et al., 1975). Following treatment at 3500, 2000 and 770 mg/m³ (810, 460 and 180 ppm), hematological parameters (blood cell counts, hematocrit and hemoglobin) of rats appeared normal when determined after 3, 7 and 13 weeks of treatment. BUN, SGOT, SGPT and SAP levels in rats were also not altered by repeated mixed xylene inhalation. Microscopic examination of tissues (lung, liver, kidney, adrenal, brain, pituitary, trachea, thyroid, parathyroid, heart, spleen, stomach, duodenum, pancreas, ileum, jejunum, colon, skeletal muscle, sciatic nerve and bone marrow) of exposed and control rats revealed no abnormalities caused by 13 weeks of exposure to the mixed xylene.

In dogs similarly exposed to 3500, 2000 and 770 mg/m³, 6 hours/day, 5 days/week for up to 13 weeks, blood cell counts and clinical chemistry evaluations showed no difference between preexposure and postexposure values. None of the three exposure groups had statistically different body weight gains, liver weights or kidney weights compared with controls. Electrocardiograms taken before and after the 13-week study were normal in all dogs (Carpenter et al., 1975).

Kushin et al. (1968) exposed groups of nine chinchilla rabbits to 200 mg/m³ (46 ppm) xylene for 2 hours/day or to 50 mg/m³ (12 ppm) for 4 hours/day for 10-12 months. During months 1-2, increases in hemoglobin content, erythrocytes, leukocytes, common proteins and gamma globulins occurred as well as increased blood acetylcholinesterase activity and excretion of 17-ketosteroids. Decreased weight gain and immunological response occurred as well. During months 4-8 of exposure, a weakening of adrenal cortex functions, disturbance of intermediary metabolism and decreased immunobiological activity occurred. The authors concluded that these changes reflected an "overstraining of defense mechanisms and adaptation systems." During the remainder of the study activity was decreased in many systems. The authors concluded that longer exposure to low concentrations of xylene rather than shorter exposure to high concentrations was associated with more pronounced changes. NIOSH (1975) commented that the significance of these results were difficult to assess because the experimental design was not adequately defined.

Fabre et al. (1960) exposed 6 rabbits to 5 mg/ℓ (1150 ppm) xylene, 8 hours/day, 6 days/week for 40-55 days and 12 rabbits and 9 rats to 3 mg/ℓ (690 ppm), 8 hours/day, 6 days/week for 110-130 days. No significant changes in the blood were observed in the rabbits and rats at the 3 mg/ℓ level. Decreases in red and white cells were observed in the rabbits dosed at the 5 mg/ℓ level. Bone marrow hyperplasia without a tendency to aplasia was observed at both concentrations. At both concentrations vascular congestion in the liver, kidney, heart, adrenals, lungs and spleen were observed through microscopic examination. Renal lesions were seen in rabbits and rats dosed at both concentrations.

Savolainen and Seppalainen (1979) exposed male Wistar rats to 300 ppm (1300 mg/m^3) of xylene, 6 hours/day, 5 days/week for up to 18 weeks. The axonal membrane lipid content relative to protein was decreased in xylene-treated rats, but the cholesterol:lipid phosphorus ratio was unchanged.

Honma et al. (1983) exposed rats to 200, 400 and 800 ppm (868, 1737 and 3474 mg/m^3) xylene by inhalation for 30 days. Acetylcholine content of the striatum and whole brain was depressed dose-relatedly in xylene-exposed rats. Xylene exposure was also associated with nondose-related changes in the content of monoamines other than acetylcholine. At 800 ppm, glutamine content was increased.

Battig and Grandjean (1964) exposed rats to xylene vapor at a mean concentration of 600 ppm (2605 mg/m³), 4 hours/day for 3 weeks. No definitive effects on avoidance testing was observed; however, exposed rats had a slightly higher percentage of correct avoidance responses during the second week. During the third week, a slightly slower rate of extinction of avoidance response was observed.

Leong et al. (1984) exposed male Sherman rats, weighing ~329 g, to 690 ppm (3.3 mg/ℓ) xylene (mixture of o-, m- and p-xylene in which the m-isomer predominates), 6 hours/day, 5 days/week for 65 days. The investigators noted slight narcosis in the xylene exposed rats. No dose-response relationship with respect to mortality was observed in the xylene-exposed rats. Gross and histological examinations revealed pulmonary edema and hemorrhage attributable to chronic murine pneumonia in exposed, as well as control rats, indicating that these effects were not considered compound-related. The changes observed in weekly body weight indicated no treatment-related effects, and no compound related effects were revealed after hematological indices and clinical chemistry were evaluated.

Lione (1981) summarized the histopathological findings in the kidneys from four different inhalation experiments. Male rats were exposed to 1.5, 3 and 6 mg/ℓ (1.5, 3.0 and 6.0 ppm) mixed xylenes for 3, 7 and 13 weeks. No clear cut difference in incidence or severity of regenerative epithelium and tubular dilatation was observed compared with controls. After 7 weeks, the incidence and severity of regenerative epithelium were slightly greater in male rats exposed to 6 mg/ℓ (6 ppm) xylene as compared with controls. In rats exposed to 3 and 6 mg/ℓ (3 and 6 ppm) of mixed xylene for 13 weeks, the incidence of low grade regenerative epithelium was greater than controls. Dogs exposed to 1.5, 3 and 6 mg/ℓ (1.5, 3.0 and 6.0 ppm) mixed xylene by inhalation did not exhibit microscopic alterations of the kidneys.

Desi et al. (1967) speculated that the effect of xylene on the CNS may lead to impaired learning and memory ability and, therefore, tested the performance of exposed rats in maze running. Two studies were conducted; the first measured the performance of rats already knowing the maze route following xylene exposure (effect on memory), while the second studied the effect of xylene on the ability of rats to learn the maze. In the first experiment, four groups of nine rats each were exposed to 0, 172, 430 or 860 mg xylene/kg/day in a saline solution by subcutaneous injection for 28 days. In the second study, 16 rats were given 430 mg xylene/kg/day by subcutaneous injection for 6 weeks. A vehicle control group of 16 rats was used for comparison. In the first study, no decrement in performance in the maze was evident, but exposed rats did show a dose-related decrease in weight gain. Four of nine animals in the group exposed at 860 mg/kg/day died on the 20th day of treatment, at which time this group was discontinued. In the second study, xylene exposure caused significantly ($p<0.02$) slower learning of the maze route. At the end of this study (6 weeks), the mean body weight of the exposed rats was decreased by 20%.

Rank (1985) studied the effects of m-xylene exposure on alpha-adrenergic receptor binding in discrete areas of the mouse brain. Female NMRI mice were exposed by inhalation to m-xylene at a level of 1600 ppm for 4 hours/day, 5 days/week for 7 weeks. At the end of the exposure, the binding of 3H-clonidine (alpha-receptor binder) was measured in the hypothalmus, diencephalon, cortex and cerebellum. Specific binding was significantly lowered in m-xylene exposed mice (6.62 pmol/g) compared with controls (7.15 pmol/g), but only in the hypothalmus. This was correlated with an induced eating and drinking response in the mice.

Mikulski et al. (1972) studied a group of 51 ship painters exposed to xylene (84-93%), toluene (6-16%) and benzene (not detectable to 2%), and used 21 unexposed workers for comparison. This study emphasized changes in urinary excretion in workers exposed to <100 ppm (<434 mg/m³) or >200 ppm (>868 mg/m³) xylene during an 8-hour shift. Creatinine excretion appeared to be elevated in workers exposed to high solvent levels. Consistent with the metabolism of xylenes, toluene and benzene, urinary glucuronic acid, hippuric acid and phenol were increased in a dose-related manner. Uric acid excretion was reduced in a dose-related manner and was attributed to a reduction in glycine available for conjugation. The authors reported no other xylene-related effects, but suggested that inhibition of uric acid production may be important in diseases that also affect the excretion of this metabolite.

Askergren et al. (1981a,b) and Askergren (1981, 1982) examined renal functions in workers exposed to various organic solvents. The study group consisted of 134 workers of whom only 40 were exposed to xylene and toluene in the manufacturing of paint. A control group of 48 unexposed workers was used. The mean concentration of urinary albumin among workers exposed to xylene and toluene (13.7 mg/ℓ or 13.7 ppm) was elevated ($p<0.05$) compared with controls (3.7 mg/ℓ or 3.7 ppm), but the median values were comparable (3.2 and 3.1 mg/ℓ, respectively). These data indicate that subjects excreting high levels of albumin were more numerous in the exposed group, but not all subjects had elevated levels. Levels of β-2-microglobulin and creatinine in the urine and osmolality of the urine were comparable between control and exposed groups (Askergren et al., 1981a). In studies testing the ability of the kidney to concentrate the urine, Askergren et al. (1981b) reported that the group (n=118) exposed to various solvents (styrene, toluene or xylene and toluene) showed no decrement in renal function.

Exposure levels of the study group were moderate, exceeding Swedish limits (styrene 170 mg/m^3, toluene 300 mg/m^3 or xylene 350 mg/m^3) by 2-3 times for only short periods, and were generally below the limits (Askergren et al., 1981b). In another study, Askergren (1981) reported the excretion of erythrocytes and leukocytes in the urine of men exposed to styrene, toluene, or xylene and toluene. In the exposed group, the average excretion of red blood cells and white blood cells in the urine was significantly elevated ($p=0.011$ and $p=0.014$, respectively) when compared with controls. The increase in urinary blood cells was attributed to glomerular damage by the different solvents. Askergren (1982) suggested that increased permeability of the glomerular basement membrane could cause increased albumin and blood cell excretion, while proximal distal tubular function (measured by concentration ability) did not appear to be affected.

Renal damage as a result of solvent exposure was also studied by Franchini et al. (1983) in workers exposed to several types of cyclic and aliphatic hydrocarbons. A group of 118 painters (predominantly males) was exposed to toluene, xylene and other benzene homologues for an average of 9.1 years. Exposure levels of xylene were not determined or estimated. Two control groups consisting of males and females (50 females and 30 males or 16 females and 65 males) were used for comparison. Excretion of albumin in the urine as a marker of increased glomerular permeability was not elevated in the exposed group. Urinary β-glucuronidase levels in exposed painters were significantly ($p<0.01$) higher than in either control group. Lysozymurea in the painters was elevated but not significantly when compared with the control groups.

The activities of liver enzymes in the serum of 102 male car painters exposed primarily to xylene and toluene were determined and compared with a group of 102 age-matched controls consisting of locomotive engineers and assistants. Overall solvent levels were reportedly about half the TLV recommended by the ACGIH (1985-1986) (435 mg/m^3 xylene; 375 mg/m^3 toluene) (Kurppa and Husman, 1982). The car painters were exposed to toluene (mean concentration of 306 ppm or 1150 mg/m^3), xylene (5.8 ppm or 25 mg/m^3) and other solvent components (butyl acetate, 6.8 ppm; white spirit, 4.9 ppm and others) for periods of 1-40 years. Effects of the solvent exposure on serum enzyme activities, neurophysiological function and ophthalmological parameters were studied. Twelve of 59 car painters examined neurophysiologically had abnormally slow motor and sensory conduction velocities and neuromuscular latencies. Lens opacities were identified in 48/92 car painters having ophthalmological examinations. The results of serum enzyme activity determinations were comparable between the exposed and control groups. The complex nature of solvent exposure in this group of workers made it difficult to determine an etiological agent. In fact, toluene may be of primary importance because of its concentration.

A group of 17 paint industry workers exposed to xylene (111 mg/m^3) and 10 other solvents was used to study the possible genotoxic activity of these solvents (Haglund et al., 1980). Peripheral lymphocytes were prepared from the painters and a group of matched controls for chromosome studies. The frequency of SCEs was nearly identical between the two groups (0.193 and 0.192 exchanges per chromosome for painters and controls, respectively). The number of chromosome aberrations (gaps, translocations, deletions, inversions, breaks, aneuploidy) among workers most extensively exposed to the solvents was also not different from their respective controls. No chromosomal abnormalities could be related to solvent exposure.

Sukhanova et al. (1969) studied the effects of workplace exposure to organic solvents (xylene was one of these) on immunocompetency, and postulated that exposure to aromatic hydrocarbons may cause leukocytopoenia. A decrease in neutrophilic glycogen content and peroxidase activity was observed in leukocytic workers, but these effects were observed in workers with normal leukocyte counts. A slight but statistically significant decrease in neutrophilic glycogen content was observed in xylene-exposed workers. A correlation between length of employment and magnitude of effect was indicated. Approximately one-third of the workers reported the following symptoms: headaches, insomnia, irritability, tachycardia and dyspepsia.

Moszychzynski (1981, 1982) and Moszychzynski and Lisiewicz (1983, 1984) studied the effects of exposure to mixed organic solvents (benzene, toluene and xylene) on the hematopoietic system. Increased reticulocyte counts were observed in workers exposed for 1-122 months. In workers exposed for 55-122 months, lowered leukocyte counts, mean corpuscular hemoglobin in erythrocytes, increased monocyte counts and decreased total lymphocyte counts were observed as well.

Dossing et al. (1983) studied a group of 156 patients admitted to a hospital for treatment of solvent intoxication or dementia from chronic occupational exposure to various solvents (white spirit, xylene, toluene and styrene). Liver injury, as indicated by increased serum aminotransferase, were found in 23 patients, as well as 11 liver steatosis cases and 6 cases of hepatic focal necrosis.

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of xylene and its isomers are reported in Table 5-4. Mice treated by inhalation may be the most susceptible species (Cameron et al., 1938). o-Xylene may be slightly more toxic by oral administration, but

TABLE 5-4

Acute Lethality of Xylenes*

Route of Exposure	Species/Strain	Sex	Number	Compound	Purity	Dose	Parameter/Effect	Reference
Oral	rat/Carworth-Wistar	M	5	m-xylene	NR	6.75 g/kg	LD_{50}	Smyth et al., 1962
Oral	rat/NS	NS	NS	o-xylene	NS	3.6 g/kg	LD_{50}	Ungvary et al., 1979b
Oral	rat/NS	NS	NS	m-xylene	NS	5.1 g/kg	LD_{50}	Ungvary et al., 1979b
Oral	rat/NS	NS	NS	p-xylene	NS	4.1 g/kg	LD_{50}	Ungvary et al., 1979b
Oral	rat/albino	F	NS	xylene	NS	6.1 g/kg	LD_{50}	Muralidhara, 1980
Oral	rat/Long-Evans	M	6	mixed xylene	NR	8.8 g/kg	LD_{50}	Hine and Zuidema, 1970
Oral	rat/Wistar	M	20	xylene	m-xylene 52% p-xylene 24% o-xylene 19%	4.3 g/kg	LD_{50}	Wolf et al., 1956
Oral	rat/NR	NR	10	o-xylene	NR	6.26 g/kg	mortality, 7/10	Gerarde, 1959
Oral	rat/NR	NR	10	m-xylene	NR	6.14 g/kg	mortality, 3/10	Gerarde, 1959
Oral	rat/NR	NR	10	p-xylene	NR	6.12 g/kg	mortality, 6/10	Gerarde, 1959
Oral	rat/NS	NS	NS	xylene	NS	9 g/kg	100% mortality	Faustov, 1960
Inhalation	mice/NR	NR	10	o-xylene	NR	saturated vapor (12,250 ppm) x 12 hours	mortality, 2/10	Cameron et al., 1938
Inhalation	mice/NR	NR	10	o-xylene	NR	6125 ppm x 24 hours	mortality, 9/10	Cameron et al., 1938
Inhalation	mice/NR	NR	10	o-xylene	NR	3062 ppm x 24 hours	mortality, 4/10	Cameron et al., 1938
Inhalation	mice/NR	NR	10	o-xylene	NR	1531 ppm x 24 hours	mortality, 0/10	Cameron et al., 1938
Inhalation	mice/NR	NR	10	m-xylene	NR	saturated vapor (8040 ppm) x 12 hours	mortality, 6/10	Cameron et al., 1938
Inhalation	mice/NR	NR	10	m-xylene	NR	2010 ppm x 24 hours	mortality, 6/10	Cameron et al., 1938
Inhalation	mice/NR	NR	10	m-xylene	NR	1005 ppm x 24 hours	mortality, 0/10	Cameron et al., 1938

TABLE 5-4 (cont.)

Route of Exposure	Species/Strain	Sex	Number	Compound	Purity	Dose	Parameter/Effect	Reference
Inhalation	mice/NR	NR	10	p-xylene	NR	saturated vapor (19,650 ppm) x 12 hours	mortality, 9/10	Cameron et al., 1938
Inhalation	mice/NR	NR	10	m-xylene	NR	4912 ppm x 24-48 hours	mortality, 0/10	Cameron et al., 1938
Inhalation	mice/NR	NR	10	m-xylene	NR	2451 ppm x 24 hours	mortality, 0/10	Cameron et al., 1938
Inhalation	rat/albino	M/F	6	m-xylene	NR	concentrated vapor	2 hours maximum exposure for no deaths	Smyth et al., 1962
Inhalation	rat/albino	M/F	6	m-xylene	NR	8000 ppm x 4 hours	mortality of 10/12	Smyth et al., 1962
Inhalation	rat/Long-Evans	M	10	mixed xylene	NR	6350 ppm x 4 hours	LC_{50}; all deaths occurring during exposure, survivors were briefly comatose	Hine and Zuidema, 1970
Inhalation	rat/Wistar	NR	10	o-xylene	NR	saturated vapor (12,250 ppm) x 12 hours	mortality, 2/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	o-xylene	NR	6125 ppm x 24 hours	mortality, 8/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	o-xylene	NR	3062 ppm x 24 hours	mortality, 1/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	o-xylene	NR	1531 ppm x 24 hours	mortality, 0/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	m-xylene	NR	saturated vapor (8040 ppm) x 12 hours	mortality, 8/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	m-xylene	NR	2010 ppm x 24 hours	mortality, 0/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	m-xylene	NR	1005 ppm x 24 hours	mortality, 0/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	p-xylene	NR	saturated vapor (19,650 ppm) x 12 hours	mortality, 8/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	p-xylene	NR	4912 ppm x 24-48 hours	mortality, 0/10	Cameron et al., 1938
Inhalation	rat/Wistar	NR	10	p-xylene	NR	2451 ppm x 24-48 hours	mortality, 0/10	Cameron et al., 1938
Inhalation	rat/NR	M	10 each dose	mixed xylene	m-xylene, 65% p-xylene, 7.8% o-xylene, 7.6% ethylbenzene, 19.3%	9900, 6000, 2800, 1300 or 580 ppm x 4 hours 6700 ppm x 4 hours	mortality, 10/10, 4/10, 0/10, 0/10, respectively calculated LC_{50}	Carpenter et al., 1975

TABLE 5-4 (cont.)

Route of Exposure	Species/Strain	Sex	Number	Compound	Purity	Dose	Parameter/Effect	Reference
Inhalation	rat/NS	NS	NS	xylene	NS	75,000 mg/m^3 (17,250 ppm) x 2 hours	100% mortality	Faustov, 1960
Inhalation	mice/SPF-OF1	F	25	m-xylene	97%	5267 ppm x 6 hours	LC_{50}	Bonnet et al., 1979
Inhalation	mice/SPF-OF1	F	25	o-xylene	98%	4595 ppm x 6 hours	LC_{50}	Bonnet et al., 1979
Inhalation	mice/SPF-OF1	F	25	p-xylene	98%	3907 ppm x 6 hours	LC_{50}	Bonnet et al., 1979
Dermal	rabbit/New Zealand	M	4	m-xylene	NR	12.4 g/kg	LD_{50}	Smyth et al., 1962
Dermal	rabbit/New Zealand	M	3	mixed xylene	NR	4.4 g/kg x 4 hours	mortality, 1/3 contact	Hine and Zuidema, 1970

*Source: U.S. EPA, 1984

NS = Not specified; NR = not reported

m- and p-xylene have been implicated as the more toxic isomers by inhalation (Cameron et al., 1938; Bonnet et al., 1979). In general, xylene has a low toxicity, with oral LD_{50} values ranging from 3.6-6.75 g/kg for the isomers and 4.3-6.1 g/kg for xylene. An LD_{50} of 12.4 g/kg was reported for rabbits (2.5-3.5 kg) exposed to xylene dermally for 24 hours (Smyth et al., 1962), suggesting that percutaneous exposure to xylene may be significant.

Olson et al. (1985) studied the effects of a co-exposure of toluene (3.25 mmol/m³) and p-xylene (2.84 mmol/m³) on CNS function. A 4-hour exposure of 16 males did not adversely affect simple reaction time, short-term memory or choice reaction time.

Effects attributable to xylene treatment have been predominantly reported in the nervous system, lungs and liver. Effects on the nervous system and lungs are usually reported after acute xylene exposure, while hepatic effects are associated with long-term exposure (U.S. EPA, 1985a).

Ogata et al. (1970) and Sikora and Gala (1957) reported that blood pressure, pulse rate, reaction time and critical flicker fusion rate were not significantly affected in 23 male volunteers exposed to 100 ppm (434 mg/m³) or 100 and 200 ppm (868 mg/m³) xylene for 3-7 hours (Ogata et al., 1970). Sikora and Gales (1957) reported that a 17-year-old overcome by xylene vapor exhibited impaired cardiac function and electrocardiographic indication of heart muscle damage.

Hake et al. (1981) studied the effects of p-xylene (99% purity, <1 ppm benzene) on male and female volunteers. Male subjects were exposed to 20, 100 and 150 ppm (87, 868 or 651 mg/m³) for 1 (n=2-3), 3 (n=2) and 7.5 (n=4) hours/day for 5 consecutive days at each exposure level. Males were sedentary except for those exposed for 7.5 hours/day, who exercised for 11 minutes on day 4 of each exposure week. Females were exposed while sedentary to 100 ppm p-xylene for 1 (n=2), 3 (n=2) or 7.5 (n=3) hours/day on 5 consecutive days. Parameters tested to identify toxic effects included hematological profile, urinalysis, EEGs, VERs, cardio-pulmonary functions, cognitive performance, time-estimation performance, coordination, visual recognition performance, arithmetic performance and subjective complaints. Measurements taken during the exposure intervals were compared with pre- and postexposure values in men and women. No significant abnormalities attributable to p-xylene exposure were reported in EEGs, VERs, pulmonary ventilation volume, heart rate, metabolic rate, blood pressure or any of the cognitive or performance tests in men or women. Except for an increased level of methylhippuric acid, urinalysis and hematology were normal. The authors did note the possible accumulation of p-xylene in the blood of males during periods of exercise with exposure at 150 ppm. Two male subjects showed a decreased performance in the Flanagan coordination test following 7.5 hours of exposure to 150 ppm p-xylene, while the other two subjects exposed at this level performed normally. This decrement in performance was not considered to be dose-related. Based on the small number of subjects, this effect cannot be attributed positively to p-xylene exposure, nor discounted as a toxic effect. Subjective complaints included eye, nose and throat irritation from one subject who wore contact lenses and from another male, both exposed for 7.5 hours at 100 and 150 ppm p-xylene. Nose and throat irritation and headache were also reported in the females exposed to 100 ppm (7.5 hours) for 5 days. Hake et al. (1981) concluded that p-xylene exposure at 100 ppm was near a NOEL in sedentary males, but sensitive individuals may experience eye and upper respiratory tract irritation. More serious effects may be seen in females or during exercise at levels near 100 ppm.

Irritation of the eyes, nose and throat was the major complaint from 10 subjects (both sexes) exposed to xylene (purity or mixture not specified) at 200 ppm for 3-5 minutes (Nelson et al., 1943). Based on these brief exposures, a majority of subjects felt that exposure at 100 ppm would be tolerable for an 8-hour workday.

Groups of six or seven human volunteers were used in a study by Carpenter et al. (1975) to determine the sensory threshold levels of mixed xylenes (65.0, 7.8, 7.6 and 19.3% m-, p-, o-xylene and ethylbenzene, respectively) when inhaled at 0.46, 1.0, 2.0 or 3.0 mg/ℓ (110, 230, 460 or 690 ppm). Volunteers inhaled the solvent at a different concentration for one 15-minute period on 4 consecutive days. No significant effects (eye or throat irritation, lacrimation, dizziness or tasting of the compound) were reported by the group of six subjects exposed to 0.46 mg/ℓ. After the 15-minute exposure at 1.0 mg/ℓ, 1/7 subjects reported eye irritation and lacrimation, tasting the solvent and dizziness. Eye irritation was the predominant complaint, reported by 4/6 subjects, following exposure at 2.0 mg/ℓ. In addition to eye and throat irritation and lacrimation, 4/6 subjects exposed to 3.0 mg mixed xylene/ℓ (690 ppm) reported dizziness. All subjects reported sensing the odor of the solvent at levels $\geq$0.06 mg/ℓ, and the average olfactory threshold level was determined to be ~0.0045 mg/ℓ (1.0 ppm) (Carpenter et al., 1975). Hake et al. (1981) also reported that p-xylene at 1.0 ppm (4.3 mg/m^3) could be detected by smell.

The effect of mixed xylene (54.4, 12.8, 12.1 and 20.7% m-, p-, o-xylene and ethylbenzene) inhalation on central nervous function was determined by the performance of male subjects in five tests (addition simple and choice reaction time, short-term memory and critical flicker fusion frequency) (Gamberale et al., 1978). Two series of experiments were conducted. In the first, three groups of five subjects each were exposed at rest to 0, 435 or 1300 mg mixed xylene/m^3 for 70 minutes and exposures were alternated every other day so that each group was exposed at all three levels. In the second experiment, eight of the same subjects were exposed to 1300 mg mixed xylene/m^3 and exercised (bicycle ergometer at 100 W work) for the first 30 minutes of the study. The xylene vapor disguised with menthol was administered by a breathing valve, and vapor concentration was monitored by hydrocarbon analyzer and gas chromatography. Performance testing was conducted during the last 35 minutes of the exposure period. In the first experiments (exposure while at rest), no significant changes in performance in any test were found in subjects exposed to 435 or 1300 mg/m^3. Following exposure to 1300 mg/m^3 and exercise, the total uptake of xylene was notably increased (1210 mg uptake vs. 180 and 541 mg, respectively, at rest) and performance in all five tests was impaired. Significant decreases ($p<0.05$) in performance were found for addition reaction time (time needed for the subject to add four displayed numbers and report the result) and short-term memory (recall and report the sequence of 4-100 numbers displayed to the subjects). The authors noted that exercise increased the uptake of xylene and presumably elevated blood levels of the solvent to a level that caused a depressant effect on neural function. It was also noted that the performance of more complex and cognitive tests showed more decrement and that neural pathways for these mental tasks may be more sensitive.

Savolainen et al. (1980a) conducted psychophysiological performance tests on eight male volunteers exposed to m-xylene at constant and varied concentrations [90-188 ppm (390-816 mg/m^3) TWA, 6 hours/day, at rest and while exercising 100 W on a bicycle ergometer]. Reaction time, manual dexterity, body balance and EEG were recorded on 5 consecutive days and 1 additional day after a 2-day no exposure period. Body balance was impaired following continuous exposure to xylene at 90 ppm (3 hours of exposure in the morning, 1 hour no exposure and 3 hours of exposure in the afternoon) on the first day of exposure and on the first day following the 2-day no exposure period. Tolerance to the xylene was evident. Reaction time and manual coordination were impaired at various random times during the exposure week. When xylene concentrations were fluctuated from 64-200 ppm (260-868 mg/m^3) with a TWA of 93 ppm (404 mg/m^3), body balance was impaired on the third day of exposure and on the fifth day when exposure levels were doubled. Only slight and random changes in the reaction times of subjects were noted throughout this exposure. Changes in the spontaneous EEG (increasing number of occipital slow transient waves) were reported in four subjects exposed to xylene when the concentrations were varied from 64-200 ppm.

The effects of m-xylene (laboratory grade) inhalation for 4 hours at ~6.5 and 11.1 μmol/ℓ (690 and 1178 mg/m^3) were tested in two groups of five male volunteers (Savolainen, 1980). Each group was tested at both exposure levels during different weeks. Blood levels of xylene and body sway, visual-manual reaction time, and tapping speed were determined before and after exposure and twice during the exposure period. Mean m-xylene blood levels reached 22.1 and 40.7 μmol/ℓ (2350 and 4320 mg/m^3) following exposure at the low and high concentrations, respectively. m-Xylene exposure at either concentration had no significant effect on the average body sway, but the maximum amplitudes of sway showed a tendency to increase following m-xylene exposure. Choice reaction time (visual stimuli converted to manual choice) was not affected by m-xylene at ~6.5 μmol/ℓ, but 11.1 μmol/ℓ showed some impairment, although not statistically significant. Simple reaction time and tapping speed were not impaired following exposure at either concentration of m-xylene (Savolainen, 1980).

In further tests of the same group of volunteers exposed on the same schedule, Savolainen et al. (1980b) also reported that the critical flicker fusion threshold (the frequency at which strobosonic light pulses appear as continuous illumination) was not impaired by xylene at the lower concentration and improved in subjects at ~11.1 μmol/ℓ (1178 mg/m^3). Extraocular muscle balance and ocular nystagmus was not affected by exposure to m-xylene at either concentration tested.

The effects of short-term m-xylene inhalation on body balance and reaction time were further examined by Riihimaki and Savolainen (1980). Male volunteers (n=22) were exposed to m-xylene for 6 hours/day on 5 consecutive days followed by a 2-day nonexposure period and 1-3 more days of exposure. Xylene concentrations were either constant [at 100 ppm (434 mg/m^3) except elevated to 200 ppm (868 mg/m^3) on the afternoon of day 5] or varied from baseline levels of 70 or 130 ppm (304 or 564 mg/m^3) to peak levels of 200 or 400 ppm (868 or 1737 mg/m^3) so that TWA concentrations were 100 or 200 ppm. Subjects were sedentary during exposure to constant levels of m-xylene and exercised during peak exposures in experiments in which m-xylene concentrations were varied. Body balance (measured by body sway amplitude) and reaction time (choice selection time) were impaired following exposures at 400 ppm in sedentary subjects. Development of tolerance to m-xylene was indicated by a decrease in the effects of exposure during later days of the week of exposure, but effects were discernible after the 2 days of no exposure. After exercise, body balance, reaction time and dexterity (Santa Ana test) were affected by m-xylene exposure when peak levels of 400 ppm were reached. The effects of m-xylene were relatively short-lived with only occasional impairment of body balance, lasting until 0.5 hours after exposure was terminated.

Savolainen et al. (1982a,b) exposed nine male volunteers, 20-25 years of age, to m-xylene at 8.2 μmol/ℓ (870 mg/m³) and measured the effect of exposure on balance and body sway. Body sway (antero-posterior and lateral movement) was determined using a strain gauge transducer attached to the platform on which subjects stood. Subjects were tested for body balance with eyes closed and opened. Because vision is important in maintaining body posture, even control subjects showed a greater amount of body sway with eyes closed. The eyes closed:eyes open ratio of body sway was used as a measure of nonvisual balance control. Exposure was 4 hours/day on 1 day/week and tests were conducted over 6 consecutive weeks. Average changes in the ratio of body sway with eyes closed:eyes open were reported for subjects during exposure days and nonexposure days (control ratio). This study showed a significant ($p<0.05$) decrease in the ratio of body sway with eyes closed vs. eyes open when compared with nonexposure values (Savolainen et al., 1982a,b). This finding was opposite that determined in an earlier study (Savolainen and Linnavuo, 1979) in which six subjects showed increased body sway after m-xylene exposure. In their earlier report, Savolainen and Linnavuo (1979) reported that m-xylene at 100 ppm (TWA with 200 ppm peaks) had no significant effect on body sway and equilibrium following 3 hours of exposure during the morning. After subsequent afternoon exposures at 200 ppm (TWA, with 400 ppm peaks), balance and body sway were significantly impaired in the anteroposterior axis ($p=0.016$) and lateral axis ($p=0.016$) when the eyes were closed. Lateral body sway was also significantly ($p=0.03$) increased when the eyes were open. Quantitatively, controls had 4.50, 2.90 and 1.48 mm of anteroposterior, lateral (eyes closed) and lateral (eyes open) movement, respectively, while subjects exposed to 100 ppm m-xylene in the morning and 200 ppm during the afternoon had 6.42, 3.72 and

1.65 mm of movement, respectively. Antero-posterior movement with eyes open was slightly but not significantly increased after m-xylene exposure. Because of the different effect of m-xylene on body sway determined in these two studies (Savolainen and Linnavuo, 1979; Savolainen et al., 1982a), it was suggested in the later publication that m-xylene may have a biphasic pattern of acute anesthetic effect. Stimulation and depression of the CNS by m-xylene may be critically dependent on brain and blood levels of the compound, therefore resulting in increased or decreased body sway at different periods (Savolainen et al., 1982a). Savolainen and Riihimaki (1981) reported that only fluctuating xylene concentrations (up to 400 ppm) could elicit an increase in the ratio of body sway with eyes closed:eyes open. This effect was attributed to the rapid rise in blood xylene levels during peak concentrations, affecting the central nervous equilibrium maintenance function but not visual pathways.

Seppalainen et al. (1981) exposed workers by inhalation to 700 or 1200 mg/m^3 xylene for 4 hours/day over 9 consecutive weeks with 6-day intervals between exposures. Xylene exposure of 1200 mg/m^3 decreased the amplitude of visual evoked potentials (VEPs).

Savolainen et al. (1980a) exposed eight healthy male subjects to either constant or fluctuating xylene concentrations of 3.7-8.2 μmol/ℓ (390-870 mg/m^3) 6 hours/day for 5 consecutive days followed by the 2 days of no exposure and 1 additional exposure day. The subjects were observed during control periods before and after exposure. Acute deleterious effects on EEG, reaction time, body balance and manual dexterity were recorded before, during and after exposure. Exercise seemed to antagonize some of these effects with the exception of EEG, which showed increased slow transients in occipital areas. When the subjects were given double exposures on the 5th day, similar or diminished responses were induced compared with the previous days, indicating a development of tolerance.

Seppalainen et al. (1980) exposed eight male 21- to 26-year-old humans to two concentrations of xylene alone (level not specified) and in combination with one dose of alcohol (0.8 g/kg bw) for 4 hours once/week and to two single doses of alcohol. This treatment regimen was repeated for 9 weeks. During weeks 5 and 9, the subjects were exposed to air alone. These days of no exposure served as controls. VEPs were recorded before and after exposure. The combination of 300 ppm (1300 mg/m^3) xylene with alcohol decreased the amplitude of VEP components with a latency of 60 and 110 millisec. At levels of 300 ppm of xylene alone or to 150 ppm (650 mg/m^3) xylene in combination with alcohol, "the change was towards the similar direction but smaller." The authors concluded alcohol potentiated the effects of xylene.

Savolainen et al. (1984) exposed nine healthy male subjects to m-xylene for 4 hours/day (3 hours in the morning and 1 hour in the afternoon with a 40-minute break between sessions). Some of the subjects exercised for 10 minutes at the beginning of the sessions and others were sedentary. The subjects were either exposed to stable m-xylene concentrations of 8.2 µmol/ℓ (870 mg/m^3) or fluctuating concentrations with peaks [16.4 µmol/ℓ (1740 mg/m^3), TWA = 8.2 µmol/ℓ]. Measurements were made before and after exposure. Body balance along the antero-posterior axis was impaired in the morning and in the afternoon at rest. Exercise antagonized this effect especially with the eyes closed. Impaired body balance along the lateral axis was significantly impaired in subjects who exercised and were exposed to fluctuating m-xylene concentrations. In subjects at rest and exposed to fluctuating m-xylene concentrations, body balance was improved, especially with eyes closed. After fluctuating exposure peaks and exercise, complex audiomotor reaction times were impaired. Changes in simple visual reaction times were similar to body balance along the a-p axis.

Savolainen et al. (1979b) exposed six male students to 4.1-8.2 μmol/ℓ (435-870 mg/m³) m-xylene for several successive days, 6 hours/day for 2 weeks. The exposure pattern was stable (4.1-8.2 μmol/ℓ) during week 1 and fluctuating (4.1-16.4 μmol/ℓ; 435-1740 mg/m³) during week 2. The subjects acted as their own controls. Inhalation of m-xylene at a concentration of 4.1 μmol/ℓ had a deleterious acute effect on reaction time performance and equilibrium in nonadapted humans. Tolerance to m-xylene developed over 5 exposure days, but the same effects were still noted the following week.

Hastings et al. (1983) exposed human subjects to xylene at levels 1-4 times the TLV. Exposed subjects had a higher incidence of eye irritation as well as an increased rate of eyeblink compared with controls. No significant effect on respiration rates or psychomotor function was observed.

5.7. SUMMARY

Xylenes (mixed isomers) have been tested for carcinogenicity in rats treated with 0, 250 and 500 mg/kg/day and mice treated with 0, 500 and 1000 mg/kg/day by gavage, 5 days/week for 103 weeks (NTP, 1986). No compound-related evidence of carcinogenicity was found, although interstitial cell tumors in male rats were observed. Maltoni et al. (1985) reported higher incidences of total malignant tumors in male and female rats treated by gavage with xylenes at 500 mg/kg/day, 4 or 5 days/week for 104 weeks than in controls. This study did not report survival or specific tumor types; therefore, the results cannot be interpreted.

Berenblum (1941) reported that xylene was not carcinogenic in skin-painting experiments in mice. Pound (1970) observed that 4/28 mice surviving 35 weeks had tumors in initiation-promotion experiments with xylene as the initiator and croton oil as the promotor. Arp et al. (1983) reported that of 15 cases of leukemia in a cohort of 6678 workers in the rubber industry, 6 of the cases occurred in employees that were exposed primarily to xylene. Exposure levels were not quantified. Based on matched case-control results, the relative risk estimate was 4.4 ($p<0.02$). Olsson and Brandt (1981) observed an increased incidence of non-Hodgkin's lymphoma in solvent-exposed workers; however, since exposure was to mixed solvents, this effect could not be attributed to xylene alone.

Mutagenicity testing of xylene in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 yielded negative results with or without metabolic activation (Florin et al., 1980; Bos et al., 1981; NTP, 1986). Negative results were also obtained in the rec assay tests in *Escherichia coli* (McCarroll et al., 1981). m- and o-Xylene were negative in the *D. melanogaster* recessive lethal test; whereas, technical xylene was weakly mutagenic. Xylene did not cause chromosomal aberrations in rats (Donner et al., 1980), and the number of chromosomal aberrations greater than control levels were not observed in a group of 17 painters exposed to xylene and 10 other solvents (Haglund, et al., 1980). The number of SCEs and structural chromosome aberrations in human lymphocytes treated with xylene *in vitro* was not significantly different from controls (Gerner-Smidt and Friedrich, 1978).

Xylene appears to be a teratogen in animals when administered by inhalation and the oral route. Marks et al. (1982) administered xylene by gavage to female mice on days 6-15 of gestation. At doses $\geq$2.06 g/kg/day, an increased incidence of cleft palate, decreased fetal weights and a significant increase in percent malformations ($p<0.05$) were observed. Maternal toxicity was also observed at these doses. The incidence of these effects was reduced at doses of 1.03 g/kg/day. Nawrot and Staples (1981) gavaged mice with either o-, m- or p-xylene 3 times/day during days 6-15 of gestation at levels of 780, 1960 and 2610 mg/kg/day. Signs of maternal toxicity and cleft palates in offspring occurred at the two highest doses of the o- and p-isomers and at the highest dose of m-xylene.

Shigeta et al. (1983) treated mice by inhalation with xylene at levels of 0, 500, 1000, 2000 and 4000 ppm (0, 2171, 4342, 8684 and 17,369 mg/m^3), 6 hours/day during days 6-12 of gestation, and observed a dose-related delay of sternebrae ossification at 2000 ppm. Hudak and Ungvary (1978) exposed pregnant CFY rats to 1000 mg/m^3 mixed xylenes continuously during days 9-14 of gestation, and observed a statistically significant increased incidence of fused sternebrae and extra ribs. Ungvary et al. (1980a) exposed rat dams to one of the xylene isomers (o-, m-, p-) continuously from days 7-14 of gestation at levels of 150, 1500 and 3000 mg/m^3. Signs of maternal toxicity were observed at 1500 mg/m^3 for the o-isomer and at 3000 mg/m^3 for the m- and p-isomers. At 3000 mg/m^3 o-xylene, skeletal retardation was observed, and at 3000 mg/m^3 m-xylene, a significant ($p<0.01$) decrease in fetal weight was observed. Skeletal retardation was observed at all doses of the p-isomer. Balogh et al. (1982) exposed rats to 230, 1900 or 3360 mg/m^3, continuously on days 7-14 of gestation, and observed delayed bone development at all three dose levels. Mirkova et al. (1983) exposed rats to a xylene mixture at levels of 0, 10, 50 or 500 mg/m^3, and observed postimplantation losses and delayed ossification at 50 and 500 mg/m^3. Teratogenic effects (hydrocephalus, microphthalmic aortal dilatation) were observed at 500 mg/m^3. Bio/Dynamics (1982) exposed both sexes of rats to 0 and 2171 mg/m³, 6 hours/day for 130 days before mating, during the mating period and on days 1-20 of gestation (females only), and observed variations in ossification and reduced female fetal weight in the offspring. Litton Bionetics (1978b) exposed rats to 0, 435 and 1737 mg/m³, 6 hours/day on days 6-15 of gestation, and observed a significant increase in retarded ossification at the high dose.

In an extensive reproduction study, male and female rats were exposed by inhalation to a xylene mixture at 0, 60, 250 or 500 ppm (0, 261, 1086 or 2171 mg/m³), 6 hours/day for 130 days before mating, during the mating period, on days 1-20 of gestation (females only) and on days 5-20 of lactation (females) (Bio/Dynamics, 1982). The only treatment-related effects were reduced pup weights and decreased mean ovary weights of female pups at day 21 after birth at 500 ppm.

Several studies concerning the toxicity of xylene by the oral and inhalation routes were located in the available literature. A dose-related increased mortality was observed in male rats treated by gavage with mixed xylenes at 250 and 500 mg/kg/day, 5 days/week for 103 weeks; the increase was statistically significant at the high dose (NTP, 1986). Many of the deaths were caused by gavage errors, but the possibility that the dosed rats resisted dosing by gavage because of a behavioral effect was not ruled out. High-dose male rats also had reduced body weight gain. Male and female mice similarly treated at 1000 mg/kg/day were consistently hyperactive for 5-30 minutes after dosing from week 4-103. In a 13-week gavage study, male and female rats treated with 1000 mg/kg/day mixed xylenes, 5 days/week had reduced body weight gain, while male and female mice treated with 2000 mg/kg/day had signs of CNS toxicity after dosing and reduced body weight gains (NTP, 1986). Bowers et al. (1982) gave male rats o-xylene at a dietary level of 200 ppm for up to 6 months and observed ultrastructural hepatocyte changes. Induction of hepatic enzyme metabolism, hepatotoxicity and hepatomegaly were observed in male rats exposed to 4750 mg/m^3 o-xylene, 8 hours/day, 7 days/week for 1 year (Tatrai et al., 1980, 1981). Jenkins et al. (1970) exposed dogs, monkeys, guinea pigs and rats to 337 and 3358 mg/m^3 o-xylene, 8 hours/day, 5 days/week for 6 weeks. No significant effects were observed in the dogs, monkeys or guinea pigs; however, 1 and 3 of 12-14 rats died in the low- and high-dose groups, respectively. Tatrai and Ungvary (1980) exposed male rats to 3500 ppm o-xylene [U.S. EPA (1984) questioned this level and suggested that the level should be 3500 mg/m^3] for 8 hours/day, 7 days/week (presumably) for 6 weeks and observed decreased body weight, hepatomegaly and ultrastructural changes. Smyth and Smyth (1928) exposed guinea pigs to 300 ppm (1300 mg/m^3) m-xylene, 4 hours/day, 6 days/week for 10 or 11 weeks. Pulmonary inflammation and slight degeneration of the liver were observed in the guinea pigs exposed for 10 weeks. Moderate renal tubular degeneration and two cases of pulmonary inflammation were observed in guinea pigs exposed for 11 weeks. Savolainen et al. (1979a) and Savolainen and Pfaffli (1980) exposed male rats to 212, 1710 and 3220 mg/m^3 m-xylene, 6 hours/day, 5 days/week for 2 and 18 weeks. The rats exposed to 212 and 1710 mg/m^3 had decreased brain glutathione and increased brain NADPH diaphorase. The rats treated at the highest dose had decreased brain glutathione and superoxide dismutase and increased NADPH diaphorase. Azoreductase activity was increased at the middle and high dose. No effects were observed in mice or rats exposed by inhalation to p-xylene at 5300 mg/m^3 or in rats exposed to 4300 mg/m^3 m-xylene or 7300 mg/m^3 o-xylene, 8 hours/day for 14 days (Cameron et al., 1938). Carpenter et al. (1975) observed no effects in rats or dogs exposed to mixed xylenes at up to 3500 mg/m³, 6 hours/day, 5 days/week for 13 weeks. Fabre et al. (1960) reported renal lesions, vascular congestion of several organs and bone marrow hyperplasia in rats and rabbits exposed by inhalation to 3000 or 5000 mg/m³. Renal tubular dilatation and epithelial regeneration were observed in rats but not dogs exposed to mixed xylene at 3000 or 6000 mg/m³.

Human occupational exposure to solvents including xylene, benzene and toluene has been associated with decreased uric acid excretion (Mikulski et al., 1972), impairment of renal function (Askergren et al., 1981a,b; Askergren, 1981, 1982), ophthalmological and neurophysiological effects (Kurppa and Husman, 1982), leukocytopenia (Sukhanova et al., 1969) and other hematological effects (Moszychzynski, 1981, 1982) and liver damage (Dossing et al., 1983). Hemopoetic cancers are discussed in Section 5.1. Results of laboratory experiments on human subjects exposed acutely by inhalation to ≥100 ppm (435 mg/m³) to xylene suggest that 100 ppm is the threshold for toxicity (Nelson et al., 1943; Carpenter et al., 1975; Riihimaki and Savolainen, 1980), although sensitive individuals may experience eye and upper respiratory tract irritation (Hake et al., 1981). The odor threshold is ~1 ppm (4.3 mg/m³) (Carpenter et al., 1975).

6. AQUATIC TOXICITY

6.1. ACUTE

The available information comparing the acute toxicity of the three xylene isomers with aquatic biota is summarized in Table 6-1. There is no clear trend in relative toxicity of the isomers. The p-isomer was most toxic to striped bass, Morone saxatilis (Benville and Korn, 1977), while the o-isomer was most toxic to Daphnia magna (Bobra et al., 1983). For a single species, differences in LC_{50} values among the isomers were generally <10-fold. The only exception was the ciliate protozoan, Colpidium colpoda, which was 100 times more sensitive to o-xylene than m-xylene (Rogerson et al., 1983).

Other acute toxicity data for fishes are presented in Table 6-2. Rainbow trout, Salmo gairdneri, and striped bass were the most sensitive of the species tested, with 96-hour LC_{50} values of 10 mg/ℓ (Folmar, 1976) and 2-11 mg/ℓ (Benville and Korn, 1977), respectively. The data of Black et al. (1982) indicate that rainbow trout larvae were the most sensitive life stage. In this study, the LC_{50} for eggs exposed throughout development (~23 days) was 5.95 mg/ℓ, and the LC_{50} for eggs and larvae exposed from fertilization to 4 days posthatching (~27 days) was 3.77 mg/ℓ.

Among invertebrates, crustaceans were generally the most sensitive species tested, having LC_{50} values of 1-10 mg/ℓ (see Tables 6-1 and 6-3).

Three studies (Folmar, 1976, 1978; Slooff et al., 1983) reported behavioral responses to xylene exposure, but the toxicological significance of these data is not apparent.

Assessing the toxicity of xylene to aquatic biota is complicated by its instability in water. Benville and Korn (1977) estimated that 20-40% of an initial xylene concentration volatilized within the first 24 hours of their

TABLE 6-1

Comparison of Acute Toxicity of Xylene Isomers to Aquatic Biota

Species	Effect	Effective Concentration of Isomer (mg/ℓ)			Reference
		m	o	p	
		FISH			
Goldfish, _Carassius auratus_	24-hour LC_{50}	16	13	18	Bridie et al., 1979b
Striped bass, _Morone saxatilis_	24-hour LC_{50}	9.2	11	2	Benville and Korn, 1977
	96-hour LC_{50}	9.2	11	2	
Guppy, _Poecilia reticulata_	7- or 14-day LC_{50}	37.7	55.1	35.1	Konemann, 1981
		CRUSTACEANS			
Water flea, _Daphnia magna_	48-hour LC_{50}	9.6	3.2	8.5	Bobra et al., 1983
	48-hour EC_{50}	14.3	8.6	8.6	Hermens et al., 1984
Bay shrimp, _Crago franciscorum_	24-hour LC_{50}	4.8	5.3	2.0	Benville and Korn, 1977
	96-hour LC_{50}	3.7	1.3	2.0	
		PROTOZOA			
Ciliate, _Colpidium colpoda_	toxicity threshold	162	1.75	NR	Rogerson et al., 1983
Ciliate, _Tetrahymena elliotti_	toxicity threshold	55.7	10.5	16.9	Rogerson et al., 1983

NR = Not reported

TABLE 6-2

Acute Toxicity of Xylene to Fishes and Amphibians

Species	Xylene Isomer/Grade	Concentration (mg/ℓ)	Effect	Reference
Rainbow trout, *Salmo gairdneri*	emulsified	7.1	2 hours, 100% survived	Walsh et al., 1977
		16.0	2 hours, 100% mortality	
	technical grade	0.01	significant attractant effect	Folmar, 1976
		0.1	significant repellant effect	
		10.0	96-hour LC_{50}, fry	
		2.0	threshold for changes in respiratory frequency	Slooff, 1979
	m-xylene	5.95	LC_{50} for embryos	Black et al., 1982
		3.77	LC_{50} for embryo-larval stages	
Coho salmon, *Oncorhynchus kisutch*	o-xylene	0.7	median avoidance level	Maynard and Weber, 1981
Goldfish, *Carassius auratus*	analytical reagent	17.0	96-hour LC_{50}	Brenniman et al., 1976
		36.8	96-hour LC_{50}	Pickering and Henderson, 1966
Carp, *Cyprinus carpio*	unspecified	1,080	24-hour LC_{50}	Rao et al., 1975
		950	48-hour LC_{50}	
		780	96-hour LC_{50}	
Fathead minnow, *Pimephales promelas*	unspecified	26.7	96-hour LC_{50}, soft water	Pickering and Henderson, 1966
		28.8	96-hour LC_{50}, hard water	Pickering and Henderson, 1966
		42.0	24-, 48-, 72- and 96-hour LC_{50}	Mattson et al., 1976
Guppy, *Poecilia reticulata*	unspecified	34.7	96-hour LC_{50}	Pickering and Henderson, 1966
Bluegill, *Lepomis macrochirus*	unspecified	20.9	96-hour LC_{50}	Pickering and Henderson, 1966
Zebrafish, *Brachydanio rerio*	unspecified	20.0	48-hour LC_{50}	Slooff, 1979
Golden orfe, *Leuciscus idus*	unspecified	43,264	48-hour LC_{0}	Junke and Luedemann, 1978
		86,308	48-hour LC_{50}	
		103,352	48-hour LC_{100}	
Cod, *Gadus morhua* (eggs)	m- or p-xylene	>10	decrease in fertilization rate	Kjoersvik et al., 1982
		2-7	effects on early cleavage pattern of eggs	
		8-15	incomplete or uneven cleavage	
		16-35	small cells or absence of cleavage	
Leopard frog, *Rana pipiens*	m-xylene	4.06	LC_{50} for eggs (5 days)	Black et al., 1982
		3.53	LC_{50} for eggs and tadpoles (9 days)	

TABLE 6-3

Acute Toxicity of Xylene to Aquatic Invertebrates

Species	Xylene Isomer/Grade	Concentration (mg/ℓ)	Effect	Reference
		CRUSTACEANS		
Dungeness crab, *Cancer magister*	o-xylene	6.0	96-hour LC_{50}, larvae	Caldwell et al., 1977
Water flea, *Daphnia magna*	unspecified	100	24-hour LC_0	Bringmann and Kuehn, 1977a
		150	24-hour LC_{50}	
		137	24-hour EC_0, immobilization	Bringmann and Kuehn, 1982
		165	24-hour EC_{50}, immobilization	
		200	24-hour EC_{100}, immobilization	
		2.1	16-day LC_{50}	Dowden and Bennett, 1965
	m-xylene	>100, <1000	24-hour LC_{50}	Tatem et al., 1978
Grass shrimp, *Palaemonetes pugio*	unspecified	14	24-hour LC_{50}	Tatem et al., 1978
		8.5	48-hour LC_{50}	
		7.5	96-hour LC_{50}	
		INSECTS		
Mosquito, *Aedes aegypti*	reagent grade	13.94	24-hour LC_{50}	Berry and Brammer, 1977
Mayfly, *Ephemerella walkeri*	emulsified	>10	avoidance	Folmar, 1978
		MOLLUSCS		
Freshwater mussel, *Dreissana polymorpha*	unspecified	11.9-19.4	detection limit, valve closure response	Slooff et al., 1983
		PROTOZOA		
Flagellate, *Chilomonas paramecium*	unspecified	>80	toxicity threshold	Bringmann et al., 1980
Flagellate, *Entosiphon sulcatum*	unspecified	>160	toxicity threshold	Bringmann and Kuehn, 1981
Ciliate, *Uronema parduczi*	unspecified	>160	toxicity threshold	Bringmann and Kuehn, 1981

bioassay, and >99% was lost after 96 hours. Dunstan et al. (1975) reported that xylene concentrations in their algal bioassay were 5-15% of the initial concentrations after 3 days growth. This explains why most mortalities observed in the Benville and Korn (1977) bioassays occurred in the first 24 hours, and why there was no difference between 24- and 96-hour LC_{50} values for striped bass. It is, therefore, difficult to establish criteria for ambient concentrations of xylene in the environment when most laboratory data are based on nominal or initial rather than measured xylene concentrations.

6.2. CHRONIC

Black et al. (1982) exposed eggs and larvae of rainbow trout and leopard frogs, Rana pipiens, to m-xylene from fertilization until 4 days posthatching. Hatchability and survival were slightly decreased in rainbow trout exposed to 2.68 mg/ℓ and significantly decreased in those exposed to 8.41 and 21.8 mg/ℓ. Hatchability and survival of leopard frog tadpoles were slightly decreased at 1.43 and 3.16 mg/ℓ and significantly decreased at 33.6 mg/ℓ.

6.3. PLANTS

Kauss and Hutchinson (1975) studied the effects of o-xylene on the green alga, Chlorella vulgaris. Concentrations of 25, 50 or 100 mg/ℓ caused a lag in culture growth, while 171 mg/ℓ inhibited growth and was lethal to cells. The concentration that would cause a 50% decrease in cell numbers was calculated to be 55 mg/ℓ. Hutchinson et al. (1980) reported EC_{50} values for inhibition of photosynthesis in Chlorella vulgaris and Chlamydomonas angulosa of 105.1 and 45.6 mg/ℓ of p-xylene, respectively. Dunstan et al. (1975) reported that reagent-grade xylene, as a mixture of three isomers, had no effect on culture growth of the aglae, Amphidium carterae, Criccosphaera carterae, Dunaliella tertiolecta or Skeletonema costatum at concentrations <10 mg/ℓ. Growth of the latter three species was significantly reduced at 10 and 100 mg/ℓ. Bringmann and Kuehn (1977b, 1978) reported that toxicity thresholds for inhibition of cell multiplication were >200 mg/ℓ xylene for blue-green alga, Microcystis aeruginosa, green alga, Scenedesmus quadricauda, and bacteria, Pseudomonas putida.

6.4. RESIDUES

Ogata and Miyake (1973) studied the uptake of xylenes by eels exposed for 1 week to seawater containing 13 mg/ℓ m-xylene, 14 mg/ℓ o-xylene, and an unspecified concentration of p-xylene. The mean xylene concentrations in liver were 21.7, 25.0 and 30.1 mg/kg, for m-, o- and p-xylene, respectively. Muscle concentrations were 5.2., 6.1 and 26.6 mg/kg for m-, o- and p-xylene, respectively. Muscle BCFs were 1.5 for m-xylene and 1.9 for o-xylene. In another experiment, Ogata and Miyake (1978) determined BCFs for the three xylene isomers in eels, Anguilla japonica, reared for 10 days in seawater containing a crude oil suspension. The BCFs were 23.6 for m- and p-xylene and 21.4 for o-xylene. In a similar study with the same species, BCFs were 27.8 for m- and p-xylene and 25.6 for o-xylene (Ogata and Miyake, 1975). BCFs for goldfish reared in aquaria containing 1 mg/ℓ of each of the three xylene isomers were 14.8 for m- and p-xylene and 14.1 for o-xylene (Ogata et al., 1984). Ferrario et al. (1985) reported that oysters, Crassostrea virginica, collected from the Inner Harbor Navigation Canal of Lake Pontchartrain, LA, contained xylene at an average concentration of 16 ppb (ng/g wet weight). Walsh et al. (1977) reported that fillets of rainbow trout exposed to 7.1 mg/ℓ emulsified xylene for 2 hours or 0.36 mg/ℓ for 56 days had an "off-flavor." Funasaka et al. (1975) found that the threshold for fish muscle to have an offensive odor was 0.02 ppm.

6.5. SUMMARY

The limited acute toxicity data for the three xylene isomers do not indicate a clear trend in relative toxicity. Rainbow trout and striped bass were the most sensitive fish species tested, with 96-hour LC_{50} values of 10 mg/ℓ (Folmar, 1976) and 2-11 mg/ℓ (Benville and Korn, 1977), respectively. The larvae of rainbow trout appeared to be more sensitive to xylene than eggs or fry (Black et al., 1982). Among the invertebrate species tested, crustaceans, with LC_{50} values of 1-10 mg/ℓ, were generally more sensitive than insects, molluscs or protozoa. There was little information available concerning chronic toxicity, plant effects or residues of xylene in aquatic biota.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

An ADI of 0.062 mg/kg/day was derived by U.S. EPA (1985a) from the study by Jenkins et al. (1970), using an uncertainty factor of 1000 for a multiple species subchronic inhalation NOEL. A second value, 0.01 mg/kg/day, was derived by U.S. EPA (1984) from the study by Bowers et al. (1982), using an uncertainty factor of 1000 for a rat subchronic to chronic oral NOAEL of 10 mg/kg/day. Higher doses were not tested.

NIOSH (1975) recommended a 100 ppm (435 mg/m^3) TWA and 10 minute ceiling at 200 ppm for the workplace. ACGIH (1985-1986) adopted a TLV of 100 ppm (~435 mg/m^3) with a STEL of 150 ppm (~655 mg/m^3) to protect against irritant effects, narcosis and possible chronic injury. WHO/FAO (1981) tentatively recommended a TWA concentration of 215 mg/m^3 pending more information concerning teratogenic effects. The OSHA Standard for xylene is 435 mg/m^3 (OSHA, 1985).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic ecosystems from xylene could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Xylenes (mixed isomers) have been tested for carcinogenicity in rats treated with 0, 250 and 500 mg/kg/day and mice treated with 0, 500 and 1000 mg/kg/day by gavage, 5 days/week for 103 weeks (NTP, 1986). No evidence of carcinogenicity was found. Maltoni et al. (1985) reported higher incidences (compared with controls) of total malignant tumors in male and female rats treated by gavage with xylene at 500 mg/kg/day, 4 or 5 days/week for 104 weeks. This study did not report survival or specific tumor types; therefore, the results cannot be interpreted. Berenblum (1941) reported that xylene was not carcinogenic in skin-painting experiments in mice. Pound (1970) reported negative results in initiation-promotion experiments with xylene as the initiator and croton oil as the promotor. Arp et al. (1983) reported that of 15 cases of leukemia in a cohort of 6678 workers in the rubber industry, 6 of the cases occurred in employees who had been exposed to coal-tar derived naphtha, which was composed primarily of xylene. Exposure levels were not quantified. Based on matched case-control results, the relative risk estimate was 5.5 ($p<0.02$); however, because of the small sample size used to calculate the relative risk and because exposure was to a mixture of solvents, these data are inadequate for risk assessment. Olsson and Brandt (1981) observed an increased incidence of non-Hodgkin's lymphoma in solvent-exposed workers; however, since exposure was to mixed solvents, this effect could not be attributed to xylene alone.

Mutagenicity testing of xylene in _S_. _typhimurium_ strains TA98, TA100, TA1535 and TA1537 yielded negative results with and without metabolic activation (Florin et al., 1980; Bos et al., 1981). Negative results were also obtained in the rec assay in _E_. _coli_ (McCarroll et al., 1981).

m-Xylene and o-xylene were negative in the _D_. _melanogaster_ recessive lethal test; whereas, technical xylene was weakly mutagenic. Xylene did not cause chromosomal aberrations in rats (Donner et al., 1980), and numbers of chromosomal aberrations greater than control levels were not observed in a group of 17 painters exposed to xylene and 10 other solvents (Haglund et al., 1980). The number of SCEs and structural chromosome aberrations in human lymphocytes treated with xylene _in vitro_ was not significantly different from controls (Gerner-Smidt and Friedrich, 1978).

Xylene appears to be teratogenic in animals at maternally toxic doses when adminisered by inhalation and the oral route. Marks et al. (1982) administered xylene by gavage to female mice between days 6 and 15 of gestation. At doses $\geq$2.06 g/kg/day, an increased incidence of cleft palate, decreased fetal weights and a significant increase in percent malformations ($p<0.05$) were observed. Maternal toxicity was also observed at these doses. The incidence of these effects was reduced at doses of 1.03 g/kg/day. Nawrot and Staples (1981) gavaged mice with either o-, m- or p-xylene 3 times/day during days 6-15 of gestation at levels of 780, 1960 and 2610 mg/kg/day. Signs of maternal toxicity and cleft palates in offspring occurred at the two nighest doses of the o- and p-isomers and at the highest dose of m-xylene.

Shigeta et al. (1983) treated mice by inhalation with xylene at levels of 0, 500, 1000, 2000 and 4000 ppm (0, 2171, 4342, 8684 and 17,369 mg/m^3), 6 hours/day during days 6-12 of gestation, and observed a dose-related delay of sternebrae ossification at 2000 ppm. Hudak and Ungvary (1978) exposed pregnant CFY rats to 1000 mg/m^3 mixed xylenes continuously on days 9-14 of gestation, and observed a statistically significant increased incidence of fused sternebrae and extra ribs. Ungvary et al. (1980a) exposed rat dams to one of the xylene isomers (o-, m-, p-) continuously from days 7-14 of gestation at levels of 150, 1500 and 3000 mg/m^3. Signs of maternal toxicity were observed at 1500 mg/m^3 for the o-isomer and at 3000 mg/m^3 for the m- and p-isomers. At 3000 mg/m^3 o-xylene, skeletal retardation was observed, and at 300 mg/m^3 m-xylene, a significant ($p<0.01$) decrease in fetal weight was observed. Skeletal retardation was observed at all doses of the p-isomer. Balogh et al. (1982) exposed rats to 230, 1900 or 3360 mg/m^3, continuously on days 7-14 of gestation, and observed delayed bone development at all three dose levels. Mirkova et al. (1983) exposed rats to a xylene mixture at levels of 0, 10, 50 or 500 mg/m^3, and observed delayed ossification at the 50 and 500 mg/m^3. Teratogenic effects (hydrocephalus; microphthalmic aortal dilatation) were also observed at 500 mg/m^3. Bio/Dynamics (1982) exposed both sexes of rats to 0 and 2171 mg/m^3, 6 hours/day for 130 days before mating, during the mating period and on days 1-20 of gestation (females only) and observed variations in ossification and reduced female fetal weight in the offspring. Litton Bionetics (1978b) exposed rats to 0, 435 and 1737 mg/m^3, 6 hours/day on days 6-15 of gestation and observed a significant increase in retarded ossification at the high dose.

In an extensive reproduction study, male and female rats were exposed by inhalation to a xylene mixture at 0, 60, 250 or 500 ppm (0, 261, 1086 or 2171 mg/m^3) 6 hours/day for 130 days before mating, during the mating period, on days 1-20 of gestation (females only) and on days 1-20 of lactation (females only) (Bio/Dynamics, 1982). The only treatment-related effects were reduced pup weights and decreased mean ovary weights of female pups at 21 days after birth.

Several studies concerning the toxicity of xylene by the oral and inhalation routes were located in the available literature. A dose-related increased mortality was observed in male rats treated by gavage with mixed xylenes at 250 and 500 mg/kg/day, 5 days/week for 103 weeks; the increase was statistically significant at the high dose (NTP, 1986). Many of the deaths were caused by gavage errors, but the possibility that the dosed rats resisted dosing by gavage because of a behavioral effect was not ruled out. High-dose male rats also had reduced body weight gains. Male and female mice similarly treated at 1000 mg/kg/day were consistently hyperactive for 5-30 minutes after dosing from week 4-103. In a 13-week gavage study, male and female rats treated with 1000 mg/kg/day mixed xylenes, 5 days/week had reduced body weight gain, while male and female mice treated with 2000 mg/kg/day had signs of CNS toxicity after dosing and reduced body weight gains (NTP, 1986). Bowers et al. (1982) gave male rats o-xylene at a dietary level of 200 ppm for up to 6 months and observed ultrastructural hepatocyte changes. Induction of hepatic enzyme metabolism, hepatotoxicity and hepatomegaly were observed in male rats exposed to 4750 mg/m^3 o-xylene, 8 hours/day, 7 days/week for 1 year (Tatrai et al., 1980, 1981). Jenkins et al. (1970) exposed dogs, monkeys, guinea pigs and rats to 337 and 3358 mg/m^3 o-xylene, 8 hours/day, 5 days/week for 6 weeks. No significant effects were observed in the dogs, monkeys or guinea pigs; however, 1 and 3 rats of 12-14 died in the low- and high-dose groups, respectively. Tatrai and Ungvary (1980) exposed male rats to 3500 ppm [U.S. EPA (1985a) questioned this level and suggested that the level should be 3500 mg/m^3] for 8 hours/day, 7 days/week (presumably) for 6 weeks and observed decreased body weight, hepatomegaly and ultrastructural changes. Smyth and Smyth (1928) exposed guinea pigs to 300 ppm (1300 mg/m^3) m-xylene, 4 hours/day, 6 days/week for 10 or 11 weeks. Pulmonary inflammation and slight degeneration of the liver were observed in the guinea pigs exposed for 10 weeks. Moderate renal tubular degeneration and two cases of pulmonary inflammation were observed in the guinea pigs exposed for 11 weeks. Savolainen et al. (1979a) and Savolainen and Pfaffli (1980) exposed male rats to 212, 1710 and 3220 mg/m³ m-xylene, 6 hours/day, 5 days/week for 2 and 18 weeks. The rats exposed to 212 and 1710 mg/m³ had decreased brain glutathione and increased brain NADPH diaphorase. The rats treated at the highest dose had decreased brain glutathione and superoxide dismutase and increased NADPH diaphorase. Azoreductase activity was increased at the middle and high dose.

Human occupational exposure to solvents including xylene, benzene and toluene has been associated with decreased uric acid excretion (Mikulski et al., 1972), impaired renal function (Askergren et al., 1981a,b; Askergren, 1981, 1982), ophthalmological and neurophysiological effects (Kurppa and Husman, 1982), leukocytopenia (Sukhanova et al., 1969) and other hematological effects (Moszychzynski, 1981, 1982), and liver damage (Dossing et al., 1983).

Results of laboratory experiments on human subjects exposed acutely by inhalation to ≥100 ppm (435 mg/m³) xylene suggest that 100 ppm is the threshold for toxicity (Nelson et al., 1943; Carpenter et al., 1975; Riihimaki and Savolainen, 1980), although sensitive individuals may experience eye and upper respiratory tract irritation (Hake et al., 1981). The odor threshold is ~1 ppm (4.3 mg/m³) (Carpenter et al., 1975). Since the NTP (1986) study indicated no evidence of carcinogenicity, it is appropriate to derive an ADI.

As indicated in Chapter 7, two ADIs have been calculated for the xylenes. U.S. EPA (1984) used the study by Bowers et al. (1982), in which rats were treated with o-xylene in the diet at 200 ppm for 6 months.

The ultrastructural changes in the liver do not appear to be adverse; therefore, the 200 ppm level was considered to be a subchronic oral NOAEL. Assuming that a rat consumes a daily amount of food equal to 5% of its body weight, 200 ppm is equivalent to 10 mg/kg/day. Dividing the NOAEL by an uncertainty factor of 1000 results in an ADI of 0.01 mg/kg/day or 0.7 mg/day for a 70 kg human.

As discussed by U.S. EPA (1985a), however, major weaknesses in the study by Bowers et al. (1982) limit its use for quantitative risk assessment. These weaknesses include the use of aged rats, the lack of monitoring of xylene loss from volatilization, the use of a single exposure level and the lack of histological examination of organs other than the liver.

U.S. EPA (1985a) chose the inhalation study by Jenkins et al. (1970) as the most appropriate basis for the ADI. In this study, rats, guinea pigs, monkeys and dogs were exposed to o-xylene at 3358 mg/m³, 8 hours/day, 5 days/week for 6 weeks or at 337 mg/m³ continuously for 90 days. Deaths occurred in the rats and monkeys, and tremors occurred in the dogs at the high repeated exposure. No effects were observed in the 337 mg/m³ continuous exposure group. The study by Carpenter et al. (1975) provides a higher NOEL of 3500 mg/m³, 6 hours/day, 5 days/week for 13 weeks in rats and dogs exposed by inhalation to mixed xylenes. This study, however, did not test as many species nor expose the animals continuously as did the study by Jenkins et al. (1970). The ADI was calculated as follows:

$$\text{ADI} = \frac{337\ \text{mg/m}^3 \times 20\ \text{m}^3\text{/day} \times 0.64}{1000} = 4.31\ \text{mg/day}$$

where: 337 mg/m³ = NOEL

20 m³ = assumed volume of inspired air/day by an adult human

0.64 = absorption factor (see Section 4.1.)

1000 = uncertainty factor

The NTP (1986) gavage bioassay was not available at the time that the documents by U.S. EPA (1984, 1985a) were prepared. This study provides further information regarding the toxicity of xylenes administered chronically by the oral route. Rats were treated with 250 and 500 mg/kg/day, 5 days/week and mice were treated with 500 and 1000 mg/kg/day. Hyperactivity, a manifestation of CNS toxicity, was observed in high-dose mice. Dose-related increased mortality and decreased body weight, which were significant at the high dose, were observed in male rats. Although many of the deaths were due to gavage error, NTP (1986) did not rule out the possibility that the rats were resisting gavage dosing because of a behavioral effect of xylene. Although mortality was also increased in the 250 mg/kg/day rats, the increase was not significant and there were no compound-related histopathological lesions in any of the treated rats or mice; therefore, the 250 mg/kg/day dose can be considered a chronic oral NOAEL. Expanding the dose over a 7-day week and dividing by an uncertainty factor of 100 (10 for interspecies extrapolation, 10 to protect the most sensitive individuals of the human population) results in an RfD for oral exposure of 1.8 mg/kg/day or 126 mg/day for a 70 kg human. This RfD is preferred over the RfDs (ADIs) derived from inhalation data because of uncertainties involved in route-to-route extrapolation and from the dietary subchronic study of Bowers et al. (1982). The RfD of 1.8 mg/kg/day (126 mg/day) should also be protective against the fetotoxicity and teratogenicity observed in the offspring of mice dosed orally during gestation because the NOAEL is well below the doses of 1960 mg/kg/day (Nawrot and Staples, 1981) and 2060 mg/kg/day (Marks et al., 1982) at which effects were observed and also because these effects were observed at doses that were associated with maternal toxicity. This

RfD should be considered provisional pending the results of ongoing subchronic oral toxicity testing by OSW (individual isomers) and OTS (mixed xylenes). If necessary, the current risk assessment will be revised to reflect the most current and appropriate data.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The fetotoxic, teratogenic, subchronic and chronic effects of oral and inhalation exposure to xylene were discussed in Sections 5.3. and 5.5. and are summarized in Table 9-1. As seen from Table 9-1, the most severe effects of xylene exposure are the increased mortality in male rats treated by gavage for 2 years in the NTP (1986) study and the teratogenic effects reported by Mirkova et al. (1983), which warrant RV_es of 10. The reliability of the Mirkova et al. (1983) study is questionable, however, because the methodology was incompletely described and because they report severe effects in rats at inhalation exposures considerably lower than those reported in numerous other studies. Therefore, the Mirkova et al. (1983) is not considered appropriate for RQ determination.

Multiplying the equivalent human dose of 65 mg/kg/day, at which male rats had increased mortality, by 70 kg results in an MED of 4550 mg/day, which corresponds to an RV_d of 1 (Table 9-2). Multiplying the RV_d by the RV_e results in a CS of 10, which corresponds to an RQ of 1000. Less severe effects that occurred at higher doses would result in lower CSs, which, therefore, need not be calculated.

The next most severe effect occurring at an equivalent chronic human dose <65 mg/kg/day is the fetotoxicity in rats observed by Ungvary et al. (1980a) at 16 mg/kg/day. The RV_e is 8. The MED of 1120 is calculated by multiplying the dose by 70 kg. The RV_d is 1, the CS is 8 and the RQ is 1000 (see Table 9-2).

The next most severe effect at doses <16 mg/kg/day is the renal tubule and liver degeneration observed by Smyth and Smyth (1928) at 2 mg/kg/day.

TABLE 9-1

Toxicity Summary for Xylene

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Isomer	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Chronic Human Dose^a (mg/kg/day)	Response	Reference
Oral	rat/Long-Evans	M	20	0.8-0.9^b	diet	o-xylene	200 ppm in diet for 6	10^c	2.3	Ultrastructural hepatocyte changes	Bowers et al., 1982
Oral	rat/F344	M	50	0.425 (M)^d	corn oil	mixed xylenes	500 mg/kg/day, 5 days/week, 103 weeks	357^e	65	Decreased body weight gain, increased mortality	NTP, 1986
Oral	rat/F344	M,F	10/sex	~0.19 (M)^d 0.14 (F)^d	corn oil	mixed xylenes	1000 mg/kg/day, 5 days/week, 13 weeks	714^e	10.0 (M) 9.0 (F)	Decreased body weight gain (did not occur at lower doses in chronic study)	NTP, 1986
Oral	mouse/ B6C3F1	M,F	50/sex	0.04 (M)^d 0.033 (F)^d	corn oil	mixed isomers	1000 mg/kg/day, 5 days/week, 103 weeks	714^e	59 (M) 56 (F)	Consistently hyperactive for 5-30 minutes after dosing from week 4-103 (acute response)	NTP, 1986
Oral	mouse/ B6C3F1	M,F	10/sex	0.028 (M)^d 0.022 (F)^d	corn oil	mixed isomers	2000 mg/kg/day, 5 days/week, 13 weeks	1429^e	10.5 (M) 9.7 (F)	Signs of CNS toxicity, reduced body weight gain (did not occur at lower doses in chronic study)	NTP, 1986
Oral	mouse/CD-1	F	26	0.03	gavage/ cottonseed oil	mixed xylene	2060 mg/kg/day during gestation	2060	155	Fetal: 6 cleft palates; 1 exencephaly; significantly increased ($p<0.01$) percent malformations. Increased liver weights in dams	Marks et al., 1982
Oral	mouse/NR	F	NR	0.03	NR/ gavage	o-, m- or p-xylene	1960 and 2610	1960 and 2610	148 and 197	Maternal toxicity; increased resorptions; cleft palates	Nawrot and Staples, 1981
Inhalation	rat/CFY	M	30	0.35^f	air	o-xylene	3500 mg/m^3 for 6 weeks	743^g	12.7	Decreased body weight, hepatomegaly, ultrastructural hepatocyte changes	Tatrai and Ungvary, 1980

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Isomer	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Chronic Human Dose[a] (mg/kg/day)	Response	Reference
Inhalation	rat/CFY	M	NR	0.35[f]	air	o-xylene	4750 mg/m³ 8 hours/day, 7 days/week for 1 year	1009[g]	173	Hepatomegaly; decreased body weight, increased water and food consumption; hepatotoxicity and induction of hepatic enzyme metabolism	Tatrai et al., 1980, 1981
Inhalation	rabbit/NR	NR	6 or 12	3.8[f]	air	xylene	3000 or 5000 mg/m³ 8 hours/day, 6 days/week, 40-130 days	451 or 752[g]	17.1 or 28.5	Decreased red and white cell counts at high dose; bone marrow hyperplasia at both doses; vascular congestation of internal organs; renal lesion	Fabre et al., 1960
Inhalation	rat/NR	NR	9	0.35[f]	air	xylene	3000 mg/m³ 8 hours/day 6 days/week 110-130 days	546[g]	9.3	Renal lesions	Fabre et al., 1960
Inhalation	rat/Wistar	M	20	0.35[f]	air	xylene	300 ppm (1300 mg/m³), 6 days/week for 5, 9, 14 and 18 weeks	148[g]	2.5	Decreased brain superoxide dismutase, after 5 weeks; increased superoxide dismutase by week 18; slight decrease in behavioral activity	Savolainen et al., 1979a
Inhalation	rat/CFY	F	20	0.35[f]	air	mixed xylenes	1000 mg/m³ 24 hours/day days 9-14 of gestation	637[g]	109	Fused sternebrae, extra ribs, delayed ossification	Hudak and Ungvary, 1978
Inhalation	rat/CFY	F	20/group	0.35[f]	air	o-xylene	1500, 3000 mg/m³ 24 hours/day days 7-14 of gestation	956 and 1911[g]	163 and 327	Increased liver weight of dams; decreased fetal weight, fetal deaths and skeletal retardation at high dose	Ungvary et al., 1980a
Inhalation	rat/CFY	F	30	0.35[f]	air	m-xylene	3000 mg/m³ 24 hours/day days 7-14 of gestation	1911[g]	327	Maternal deaths, reduced fetal weight	Ungvary, et al., 1980a

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Isomer	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Chronic Human Dose^a (mg/kg/day)	Response	Reference
Inhalation	rat/CFY	F	20/group	0.35^f	air	p-xylene	150, 1500, 3000 mg/m^3 24 hours/day days 7-14 of gestation	96, 956 and 1911^g	16, 163 and 327	At highest dose: reduced litter size, reduced fetal weight, fetal resorptions. At all doses: delayed skeletal development	Ungvary, et al., 1980a
Inhalation	rat/NR	F	NR	0.35^f	air	mixed xylenes	230, 1900 or 3000 mg/m^3 24 hours/day days 7-14 of gestation	25, 1210 or 2141^g	25, 207 or 366	Delayed ossification, extra ribs, postimplantation loss	Balogh et al., 1982
Inhalation	rat/CD	M,F	20	0.35^f	air	mixed xylenes	500 ppm (2171 mg/m^3) 6 hours/day, 130 days premating and during gestation	346^g	59	Decreased fetal weight, ossification variations	Bio/Dynamics, 1982
Inhalation	rat/CFY	M	6	0.35^f	air	o-xylene	4500 mg/m^3 8 hours/day 6 days/week for 6 weeks	819^g	14.0	Increased cytochrome P-450 and b-5, increased aniline hydroxylase and aminopyrine demethylase	Ungvary et al., 1980b
Inhalation	rat/Wistar	M	NR	0.35^f	air	xylene	1300 mg/m^3 6 hours/day 5 days/week 18 weeks	150^g	2.6	Decreased axonal membrane lipid content relative to protein	Savolainen and Sappolainen, 1979
Inhalation	rat/Wistar	F	NR	0.35^f	air	xylene	10, 50 and 500 mg/m^3 6 hours/day, 5 days/week for 3 weeks during gestation	1.1, 5.7 and 57	0.19, 0.97 and 9.7	At 50 and 500 mg/m^3 statistically significant increased incidence of postimplantation losses ($p<0.05$) and hemorrhages ($p<0.01$); decreased mean fetal weight ($p<0.05$); abnormal ossification of sternum; impaired formation of skull; unspecified skeletal defects observed at 10 mg/m^3	Mirkova et al., 1983

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Isomer	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Chronic Human Dose[a] (mg/kg/day)	Response	Reference
Inhalation	guinea pigs	NR	≥3	0.84	air	m-xylene	300 ppm (1300 mg/m^3) 4 hours/ day, 6 days/week for 10 or 11 weeks	88	2.0	Slight degeneration of the liver; pulmonary inflammation, moderate renal tubule degeneration	Smyth and Smyth, 1928
Inhalation	mouse/ICR	F	NR	0.03	air	xylene	2000 ppm (8684 mg/m^3) 6 hours/ day, days 6-12 of gestation	282	21.3	Fetotoxicity; decreased fetal weight, delayed ossification	Shigeta et al., 1983

[a] Equivalent chronic human doses were calculated by multiplying the transformed animal dose by the cube root of the ratio of the average animal body weight to the reference human body weight (70 kg). Subchronic doses were divided by an uncertainty factor of 10.

[b] The rats were aged at the beginning of the study.

[c] Calculated by multiplying the dietary level by a food factor of 0.05 (U.S. EPA, 1980).

[d] Estimated from body weight data provided by NTP (1986).

[e] Calculated by expanding dose over 7-day week.

[f] Reference rat and mouse weights from U.S. EPA (1980), reference rabbit and guinea pig weights from U.S. EPA (1985b).

[g] Doses were calculated by expanding inhalation exposures over 24 hours and 7 days, when necessary, and by multiplying by the animal breathing volume and dividing by animal body weight. Breathing rates for rats and mice from U.S. EPA (1980), for rabbits and guinea pigs from Durkin (1985).

TABLE 9-2

Composite Scores for Xylene

Route	Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	rat	357	4550	1.0	Increased mortality	10	10	1000	NTP, 1986
Inhalation	rat	96	1120	1.0	Delayed skeletal development	8	8	1000	Ungvary et al., 1980a
Inhalation	guinea pig	88	140*	2.3	Slight liver and kidney degeneration	4	9.2	1000	Smyth and Smyth, 1928

*The dose was divided by 10 to approximate chronic exposure.

Multiplying by 70 results in an MED of 140 mg/day, which corresponds to an RV_d of 2.3. Because the degree of degeneration was described as slight, an RV_e of 4 is warranted. The CS of 9.2 corresponds to an RQ of 1000.

The highest CS of 10 was obtained for increased mortality of rats in the study by NTP (1986) and is recommended as the basis of the RQ for xylenes (Table 9-3).

In a previous determination of the RQ, Goetchius and Becker (1985) derived an RQ of 1000 based on the study by Marks et al. (1982), in which teratogenic effects (cleft palate, exencephaly, increased percent malformations) were observed in offspring of mice orally dosed with 2060 mg/kg/day mixed xylene during days 6-15 of gestation. Maternal toxicity (increased liver weight) was observed in the dams, an effect that warranted an RV_e of 9. The RV_d was 1. Multiplying the RV_e by the RV_d yielded a CS of 9, which corresponds to an RQ of 1000. The NTP (1986) study was not available at the time that the previous document was prepared.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Xylenes (mixed isomers) have been tested for carcinogenicity in rats treated with 0, 250 and 500 mg/kg/day and mice treated with 0, 500 and 1000 mg/kg/day by gavage, 5 days/week for 103 weeks (NTP, 1986). No compound-related evidence of carcinogenicity was found. Maltoni et al. (1985) reported higher incidences of total malignant tumors in male and female rats treated by gavage with xylenes at 500 mg/kg/day, 4 or 5 days/week for 104 weeks than in controls. This study did not report survival or specific tumor types; therefore, the results cannot be interpreted. Berenblum (1941) reported that xylene was not carcinogenic in skin-painting experiments in mice. Pound (1970) observed that 4/28 mice surviving 35 weeks had tumors in initiation/promotion experiments with xylene as the initiator and croton oil

TABLE 9-3

Xylene

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	4550 mg/day
Effect:	increased mortality
Reference:	NTP, 1986
RV_d:	1
RV_e:	10
Composite Score:	10
RQ:	1000

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*Equivalent human dose

as the promotor. Arp et al. (1983) reported that of 15 cases of leukemia in a cohort of 6678 workers in the rubber industry, 6 of the cases occurred in employees who had been exposed primarily to xylene. Exposure levels were not quantified. Based on matched case-control results, the relative risk estimate was 5.5 ($p<0.02$); however, the lack of exposure data and other confounding information preclude the use of these data for risk assessment. Olsson and Brandt (1981) observed an increased incidence of non-Hodgkin's lymphoma in solvent-exposed workers; however, since exposure was to mixed solvents, this effect could not be attributed to xylene alone.

The evidence from animal studies are inadequate to fully access the carcinogenic potential in animal test systems; human studies, while suggestive, are inconclusive and have significant confounding circumstances to render the data inadequate. Therefore, xylenes are classified as a U.S. EPA Group D compound. The lack of quantified exposure and positive animal bioassays precludes the derivation of an F factor.

Mutagenicity testing of xylene in _S_. _typhimurium_ strains TA98, TA100, TA1535 and TA1537 yielded negative results with and without metabolic activation (Florin et al., 1980; Bos et al., 1981; NTP, 1986). Negative results were also obtained in the rec assay in _E_. _coli_ (McCarroll et al., 1981). m-Xylene and o-xylene were negative in the _D_. _melanogaster_ recessive lethal test; whereas, technical xylene was weakly mutagenic. Xylene did not cause chromosomal aberrations in rats (Donner et al., 1980), and numbers of chromosomal aberrations greater than control levels were not observed in a group of 17 painters exposed to xylene and 10 other solvents (Haglund et al., 1980). The number of SCEs and structural chromosome aberrations in human lymphocytes treated with xylene _in vitro_ was not significantly different from controls (Gerner-Smidt and Friedrich, 1978).

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

In addition, the following document was obtained and examined for useful information:

U.S. EPA. 1979. The Carcinogen Assessment Group's Preliminary Risk Assessment on Xylenes. Type I - Air Program. U.S. EPA, CAG, Washington, DC.